STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 134482

TO: Zohreh Fay **Location: 3a61 / 3c70** **Tuesday, October 19, 2004** **Art Unit: 1614** **Phone: 272-0573** **Serial Number: 10 / 720688**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

Search Notes

1771100

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Zohta Kay Examiner #: 66646 Date: 10/5/04

Art Unit: 1614 Phone Number ~~3~~(571)272-0573 Serial Number: 10/772,~~222~~688

Mail Box and Bldg/Room Location: 3C70 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MEG

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Lavie, Gad

Earliest Priority Filing Date: 11/25/02

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

please search the claimed use.

Jan 12 2005

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher	NA Sequence (#)	STN ✓
Searcher Phone #: 272504	AA Sequence (#)	Dialog
Searcher Location	Structure (#)	Questel/Orbit
Date Searcher Picked Up: 10/19	Bibliographic ✓	Dr.Link
Date Completed: 10/19	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time: 20	Patent Family	WWW/Internet
Online Time: +90	Other	Other (specify)

PTO-1590 (8-01)

```
=> d his

     (FILE 'HOME' ENTERED AT 13:30:46 ON 19 OCT 2004)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 13:31:09 ON 19 OCT 2004
               E VERTEPORFIN/CN
L1             1 S E3
L2             0 S 129497-78-5/CRN
               E C41H42N4O8/MF
L3            35 S E3 AND NR>=6
L4            26 S L3 AND 11393/RID
L5            24 S L3 AND 11393.1.7/RID
L6            24 S L5 AND 9 13 DIPROPANOIC
L7            13 S L6 AND 18 ETHENYL
L8            10 S L7 AND 3 4 BIS METHOXYCARBONYL
L9            10 S L8 AND 4A 8 14 19 TETRAMETHYL
L10           10 S L9 AND ESTER
L11            3 S L10 AND IDS/CI
L12            3 S L1,L11
               E DIANTHRAQUINONE/CN
L13            1 S E4
               E C28H14O4/MF
L14            4 S E3 AND C6-C6-C6/ES AND 6/NR
               SEL RN
L15            0 S E1-E4/CRN
               E HYPERICIN/CN
L16            1 S E3
               SEL RN
L17           34 S E1/CRN
L18           11 S L17 NOT (IDS/CI OR MXS/CI OR COMPD OR WITH)
L19            9 S L18 NOT CONJUGATE

     FILE 'HCAPLUS' ENTERED AT 13:42:38 ON 19 OCT 2004
L20          974 S L14,L16,L19
L21         1148 S HYPERICIN# OR NSC407131 OR NSC()(407313 OR 407 313) OR CYCLOS
L22          291 S BIANTHRAQUINON?
L23           20 S BIANTHRACENE (L) TETRONE
L24          101 S BISANTHRAQUINON? OR PHENANTHRO?(L)PERYLEN?(L)DIONE
L25         1505 S L20-L24
L26          276 S L12
L27          176 S VISUDYNE OR CL318952 OR CL()(318952 OR 318 952) OR BPD MA
L28          175 S VERTEPORFIN?
L29          325 S L26-L28
L30            1 S US20040176345/PN OR (WO2003-US37743 OR US2002-428677# OR US20
               E LAVIE G/AU
L31           62 S E3,E4
               E LA VIE G/AU
               E PHOTODYAN/CT
               E E5+ALL
L32         7161 S E2,E3,E1+NT
               E E10+ALL
L33         4257 S E8,E9,E7
               E E6+ALL
L34         1756 S E3,E6,E7
               E PHOTOSENSITIZ/CT
L35         2076 S E11
               E E13+ALL
L36         3391 S E4,E3
               E E16+ALL
L37          959 S E5,E6,E4
               E RADIOPROTECT/CT
               E E8+ALL
```

```
L38          827 S E1
                 E E2+ALL
L39        11428 S E1+NT
L40           41 S L29 (L) ADV/RL
                 E MACULA/CT
                 E E11+ALL
L41         1097 S E2
                 E EYE, DISEASE/CT
L42         1461 S E45,E46
L43         3666 S E3+OLD,NT,PFT,RT (L) (MACULA? OR DEGENER?)
L44         2415 S E3(L)(MACULA? OR DEGENER?)
                 E EYE/CT
L45         2897 S E3+OLD,NT,PFT,RT (L) (MACULA? OR DEGENER?)
L46         2834 S E3 (L) (MACULA? OR DEGENER?)
                 E CHOROID/CT
                 E E4+ALL
L47          652 S E2
                 E RETINAL CHOROID/CT
                 E RETINA CHOROID/CT
                 E CHOROID/CT
L48          884 S (EYE# OR EYE#(L)DISEASE#)/CW  (L) CHOROID?
                 E RETINAL PIGMENT/CT
                 E E4+ALL
L49         2520 S E2
L50         2686 S (EYE# OR EYE#(L)DISEASE#)/CW  (L) PIGMENT?(L)EPITHEL?
                 E REACTIVE OXYGEN/CT
                 E E4+ALL
L51        22520 S E3
L52            8 S L25 AND L29
L53            7 S L52 AND L32-L51
L54            8 S L52,L53
L55            2 S L54 AND (EYE? OR MACULA?(L)DEGENER? OR RETINA? OR CHOROID? OR
L56            1 S L55 NOT RETINAMIDE
L57           34 S L31 AND L25,L29
L58           10 S L31 AND L32-L51
L59            9 S L57 AND L58
L60            9 S L59 AND PHOTODYN?
L61            1 S L58 NOT L60
L62           10 S L58 AND (PHOTODYNAM? OR PHOTOSENS?)
L63           10 S L58-L62
L64           25 S L57 NOT L63
                 SEL DN AN L64 25
L65            1 S L64 AND E1-E3
L66           11 S L56,L63,L65
L67           24 S L64 NOT L66
L68         6260 S L35-L37
L69         6372 S L29,L68
L70        10750 S L32-L34
L71        12254 S L38,L39
L72        24193 S L25,L70-L71
L73         5121 S L69 AND L72
L74         4165 S L73 AND (PHOTODYNAM? AND PHOTOSENS?)
L75          175 S L74 AND QUENCH?
L76           44 S L75 AND (ADV/RL OR ADVERSE EFFECT OR ?TOXIC?)
L77           43 S L76 AND RADIAT?/SC,SX
L78           19 S L77 AND ADV/RL
L79           24 S L77 NOT L78
                 SEL DN AN 7
L80            1 S L79 AND E4-E6
L81           12 S L30,L63,L65,L80 AND L20-L80

=> fil reg
FILE 'REGISTRY' ENTERED AT 15:08:21 ON 19 OCT 2004
```

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 OCT 2004 HIGHEST RN 765254-38-4
DICTIONARY FILE UPDATES: 18 OCT 2004 HIGHEST RN 765254-38-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

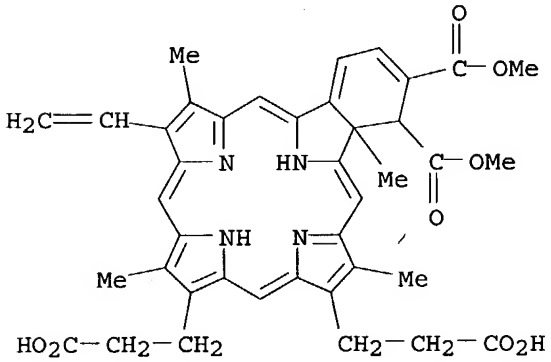
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can l12 tot

L12 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 189958-77-8 REGISTRY
CN **23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, radical ion(1-) (9CI)** (CA INDEX NAME)
MF **C41 H42 N4 O8**
CI **IDS**
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: PREP (Preparation); PROC (Process)

CM 1

CRN 189958-76-7
CMF C40 H40 N4 O8
CCI RIS



CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

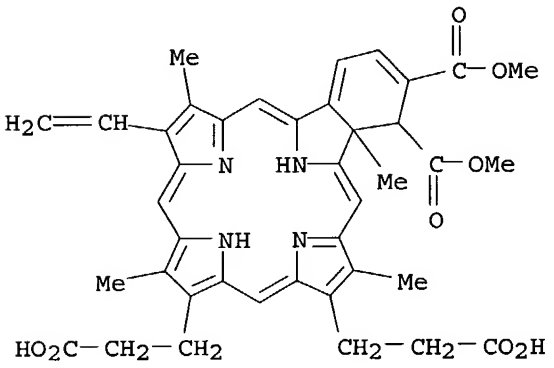
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 127:65625

L12 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 181239-64-5 REGISTRY
CN **23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester (9CI)** (CA INDEX NAME)
MF **C41 H42 N4 O8**
CI **IDS**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)

CM 1

CRN 130851-15-9
CMF C40 H40 N4 O8



CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 131:170197

REFERENCE 2: 130:51303

REFERENCE 3: 127:65625

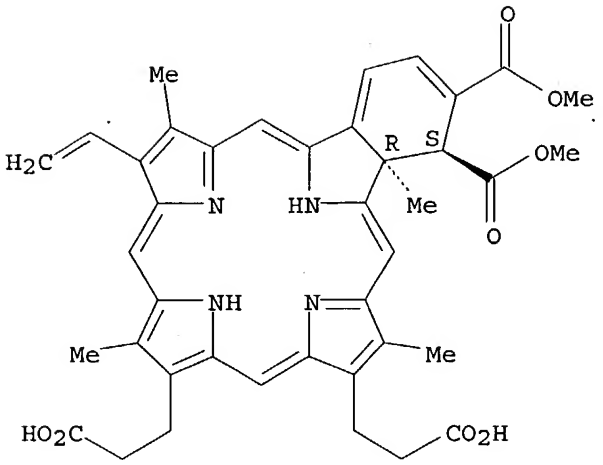
REFERENCE 4: 125:219600

L12 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 129497-78-5 REGISTRY
CN **23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, (4R,4aS)-rel- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, trans-**
OTHER NAMES:
CN **(±)-trans-3,4-Dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23H,25H-benzo[b]porphine-9,13-dipropionic acid, 3,4,9-trimethyl ester mixt. with (±)-trans-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23H,25H-benzo[b]porphine-9,13-dipropionic acid, 3,4,13-trimethyl ester**
CN BPD-MA
CN CL 318952
CN **Verteporfin**
CN Visudyne
FS STEREOSEARCH
DR 121987-00-6, 129162-83-0, 136415-38-8
MF **C41 H42 N4 O8**
CI **IDS**
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CBNB, CEN, CIN, DDFU, DIOGENES, DRUGU, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PRP (Properties); USES (Uses)

CM 1

CRN 121310-58-5
CMF C40 H40 N4 O8

Relative stereochemistry.
Double bond geometry unknown.



CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

270 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
272 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:277628

REFERENCE 2: 141:273651

REFERENCE 3: 141:254622

REFERENCE 4: 141:248487

REFERENCE 5: 141:153136

REFERENCE 6: 141:153132

REFERENCE 7: 141:153082

REFERENCE 8: 141:153052

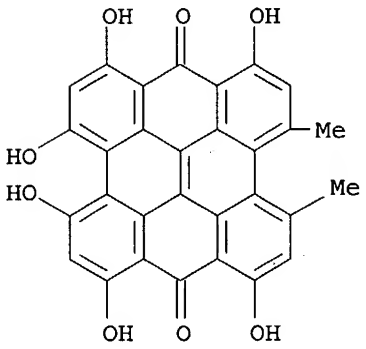
REFERENCE 9: 141:136274

REFERENCE 10: 141:128566

=> d ide can l16

L16 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 548-04-9 REGISTRY
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,3,4,6,8,13-Hexahydroxy-10,11-dimethylphenanthro[1,10,9,8-opqra]perylene-

7,14-dione P-conformer
CN Cyclo-Werol
CN Cyclosan
CN **Hypericin**
CN Hypericum red
CN NSC 407313
DR 345224-62-6
MF C30 H16 O8
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, PHAR, PROMT, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

912 REFERENCES IN FILE CA (1907 TO DATE)
43 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
914 REFERENCES IN FILE CAPLUS (1907 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:254523

REFERENCE 2: 141:238863

REFERENCE 3: 141:236353

REFERENCE 4: 141:220895

REFERENCE 5: 141:218452

REFERENCE 6: 141:202375

REFERENCE 7: 141:195281

REFERENCE 8: 141:194959

REFERENCE 9: 141:179749

REFERENCE 10: 141:153112

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:08:42 ON 19 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 19 Oct 2004 VOL 141 ISS 17
FILE LAST UPDATED: 18 Oct 2004 (20041018/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot l81

L81 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:653985 HCAPLUS
DN 141:202375
ED Entered STN: 13 Aug 2004
TI Antimetastatic activity of the **photodynamic** agent **hypericin** in the dark
AU Blank, Michael; **Lavie, Gad**; Mandel, Mathilda; Hazan, Sadick; Orenstein, Arie; Meruelo, Daniel; Keisari, Yona
CS Department of Human Microbiology, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
SO International Journal of Cancer (2004), 111(4), 596-603
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
Section cross-reference(s): 1
AB A unique property of the **photodynamic** signal transduction inhibitor **hypericin** (HY) is high functionality in the dark, which has been shown to result in portfolio of anticancer activities both in vitro and in vivo. Here we show that treatment with HY significantly reduces growth rate of metastases in 2 murine models: breast adenocarcinoma (DA3) and squamous cell carcinoma (SQ2). Focus on metastases was achieved by resection of primary tumors at stages in which

micrometastases exist in lungs. Long-term animal survival in DA3 tumor-excised groups increased from 15.6% in controls to 34.5% following supplementary treatment with HY. In mice bearing SQ2 tumor metastases, therapy with HY increased animal survival from 17.7% in controls to 46.1%. Using Laser-induced fluorescence and multipixel spectral image analyses, we demonstrate that HY has a high tendency to accumulate in primary and metastatic tumors; HY content in lungs bearing metastases was approx. 2-fold higher than in the lungs of healthy animals. The tendency of HY to preferentially concentrate in lung metastases, combined with its potent antiproliferative activities, may render HY as a useful supplementary modality in the treatment of metastatic cancer irresp. of photoactivation.

ST antimetastatic **photodynamic** agent **hypericin** dark

IT **Photodynamic action**
(absence of; antimetastatic activity of **photodynamic** agent **hypericin** in dark)

IT Mammary gland, neoplasm
(adenocarcinoma, metastasis; antimetastatic activity of **photodynamic** agent **hypericin** in dark)

IT Antitumor agents
(antimetastatic activity of **photodynamic** agent **hypericin** in dark)

IT Lung, neoplasm
(metastasis; antimetastatic activity of **photodynamic** agent **hypericin** in dark)

IT **548-04-9, Hypericin**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimetastatic activity of **photodynamic** agent **hypericin** in dark)

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

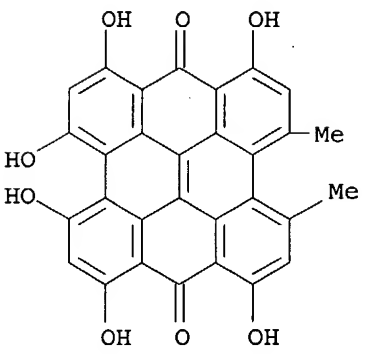
(1) Agostinis, P; Adv Enzyme Regul 2000, V40, P157 HCAPLUS
(2) Agostinis, P; Biochem Pharmacol 1995, V49, P1615 HCAPLUS
(3) Anon; Biochem Biophys Res Commun 1996, V220, P613
(4) Anon; N Engl J Med 2002, V346, P645
(5) Blank, M; Cancer Res 2003, V63, P8241 HCAPLUS
(6) Blank, M; Oncol Res 2001, V12, P409
(7) Blank, M; Photochem Photobiol 2001, V74, P120 HCAPLUS
(8) Couldwell, W; Neurosurgery 1994, V35, P705 MEDLINE
(9) Diwu, Z; Biochem Pharmacol 1994, V47, P373 HCAPLUS
(10) Erenpreisa, J; Cancer Cell Internat 2001, V1, P1
(11) Gerson, F; J Am Chem Soc 1995, V117, P11861 HCAPLUS
(12) Hostanska, K; Pharmazie 2002, V57, P323 HCAPLUS
(13) Hwang, M; Anticancer Res 2001, V21, P2649 HCAPLUS
(14) Joensuu, H; Ann Med 2001, V33, P451 HCAPLUS
(15) Lavie, G; Br J Cancer 1999, V79, P423 HCAPLUS
(16) Malik, Z; J Photochem Photobiol B:Biology 1995, V25, P213
(17) Orenstein, A; Lasers Med Sci 1998, V13, P112
(18) Redepenning, J; Photochem Photobiol 1993, V58, P532 HCAPLUS
(19) Schnier, J; Proc Natl Acad Sci U S A 1996, V93, P5941 HCAPLUS
(20) Senderowicz, A; Oncogene 2000, V19, P6600 HCAPLUS
(21) Shapiro, G; J Clin Invest 1999, V104, P1645 HCAPLUS
(22) Sotomayor, E; J Immunol 1991, V147, P2861
(23) Takahashi, I; Biochem Biophys Res Commun 1989, V165, P1207 HCAPLUS
(24) Tuveson, D; Oncogene 2001, V20, P5054 HCAPLUS
(25) Vandenbogaerde, A; J Photochem Photobiol B 1997, V38, P136 HCAPLUS

IT **548-04-9, Hypericin**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antimetastatic activity of **photodynamic** agent **hypericin** in dark)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-

10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:467729 HCAPLUS
DN 141:35598
ED Entered STN: 10 Jun 2004
TI Methods for preventing **phototoxic** damage during **photodynamic** therapy
IN **Lavie, Gad**
PA New York University, USA
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-05
CC 8-9 (**Radiation** Biochemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004047821	A1	20040610	WO 2003-US37743	20031125 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004176345	A1	20040909	US 2003-720688	20031125 <--
PRAI	US 2002-428677P	P	20021125 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004047821	ICM	A61K031-05

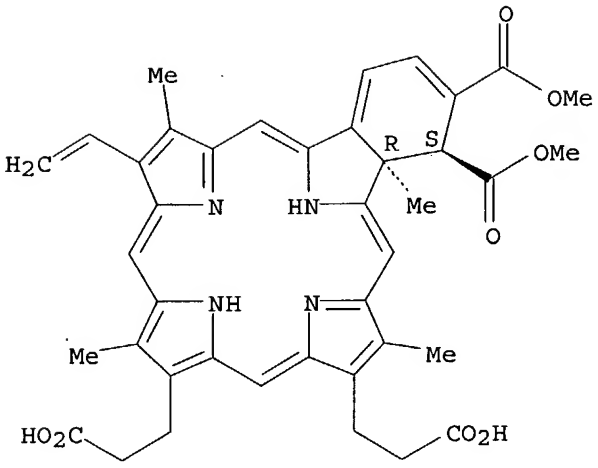
AB A method is provided for preventing or reducing the **adverse effects** of **photodynamic** therapy such as collateral damage by regulating the localized **phototoxicity** of an effector **photosensitizer** mol. During **photodynamic** therapy, the activity of the effector **photosensitizer** mol. in neighboring tissues of the tissue targeted for destruction is **quenched** by a **quenching photosensitizer** mol.
ST **hypericin dianthraquinone quencher photosensitizer phototoxic** damage **photodynamic** therapy tumor

IT **Eye**
(**choroid**; **quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT Drug delivery systems
(injections, i.v.; **quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT **Eye, disease**
(**macula, degeneration**; **quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT Blood vessel
Neoplasm
Photodynamic therapy
Photosensitizers (pharmaceutical)
Radioprotectants
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT **Reactive oxygen species**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT **129497-78-5, Verteporfin**
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT 7782-44-7D, **Oxygen, reactive species**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
IT **548-04-9, Hypericin** 220264-81-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Lavie; US 5047435 A 1991 HCAPLUS
IT **129497-78-5, Verteporfin**
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
RN 129497-78-5 HCAPLUS
CN 23H,25H-Benzo[b]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, (4R,4aS)-rel- (9CI) (CA INDEX NAME)

CM 1

CRN 121310-58-5
CMF C40 H40 N4 O8

Relative stereochemistry.
Double bond geometry unknown.

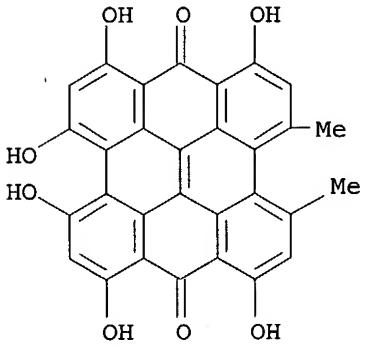


CM 2

CRN 67-56-1
CMF C H4 O

H_3C-OH

IT **548-04-9, Hypericin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**quenchers** use for preventing **phototoxic** damage during **photodynamic** therapy)
RN 548-04-9 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:755891 HCAPLUS
DN 138:1768
ED Entered STN: 06 Oct 2002
TI Wavelength-dependent properties of **photodynamic** therapy using **hypericin** in vitro and in an animal model
AU Blank, Michael; Kostenich, Genady; **Lavie, Gad**; Kimel, Sol; Keisari, Yona; Orenstein, Arie

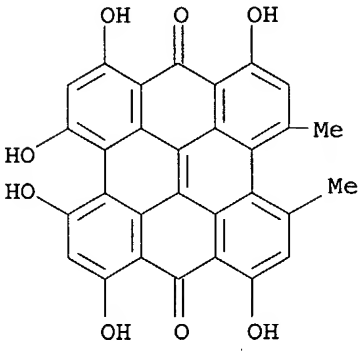
CS Department of Human Microbiology, Sackler School of Medicine, Tel Aviv University, Israel
SO Photochemistry and Photobiology (2002), 76(3), 335-340
CODEN: PHCBAP; ISSN: 0031-8655
PB American Society for Photobiology
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
AB Wavelength effects in **photodynamic** therapy (PDT) with **hypericin** (HY) were examined in a C26 colon carcinoma model both in vitro and in vivo. Irradiation of HY-sensitized cells in vitro with either 550 or 590 nm caused the loss of cell viability in a drug- and light-dose-dependent manner. The calculated ratio of HY-based PDT (HY-PDT) efficiencies at these two wavelengths was found to correlate with the numerical ratio of absorbed photons at each wavelength. In vivo irradiation of C26-derived tumors, 6 h after i.p. administration of HY (5 mg/kg), caused extensive vascular damage and tumor necrosis. The depth of tumor necrosis (d) was more pronounced at 590 than at 550 nm and increased when the light dose was raised from 60 to 120 J/cm2. The maximal depths of tumor necrosis (at 120 J/cm2) were 7.5 ± 1.5 mm at 550 nm and 9.9 ± 0.8 mm at 590 nm. Both values are rather high in view of the limited penetration of green-yellow light into the tissue. Moreover, the depth ratio, d590/d550 = 1.3 ($P < 0.001$), is smaller than expected considering the 2.2-fold lower HY absorbance and the 1.7-fold lower tissue penetration of radiation at 550 than at 590 nm. This finding indicates that in vivo the depth at which HY-PDT elicits tumor necrosis is not only determined by photophys. considerations (light penetration, number of absorbed photons) but is also influenced significantly by other mechanisms such as vascular effects. Therefore, despite the relatively short-wavelength peaks of absorption, our observations suggest that HY is an effective **photodynamic** agent that can be useful in the treatment of tumors with depths in the range of 1 cm.
ST wavelength **photodynamic** therapy **hypericin** colon carcinoma depth; irradn wavelength **hypericin** phototoxicity colon carcinoma
IT Intestine, neoplasm
(colon, carcinoma; wavelength-dependent properties of **photodynamic** therapy with **hypericin** in colon carcinoma)
IT **Phototoxicity**
(relationship between irradiation wavelength **hypericin** phototoxicity in colon carcinoma)
IT Antitumor agents
Photodynamic therapy
Photosensitizers (pharmaceutical)
Wavelength
(wavelength-dependent properties of **photodynamic** therapy with **hypericin** in colon carcinoma)
IT **548-04-9, Hypericin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(wavelength-dependent properties of **photodynamic** therapy with **hypericin** in colon carcinoma)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Agostinis, P; Adv Enzyme Regul 2000, V40, P157 HCAPLUS
(2) Anon; Opticalthermal Response of Laser-irradiated Tissue 1995
(3) Blank, M; Oncol Res 2001, V12, P409
(4) Canti, G; Anticancer Drugs 1992, V3, P139 HCAPLUS
(5) Chen, B; Cancer Lett 2000, V150, P111 HCAPLUS
(6) Chen, B; Int J Cancer 2001, V93, P275 HCAPLUS
(7) Chen, B; Int J Cancer 2002, V98, P284 HCAPLUS
(8) Chung, P; Laryngoscope 1994, V104, P1471 HCAPLUS

(9) Diwu, Z; Free Radic Biol Med 1993, V14, P209 HCAPLUS
(10) Fingar, H; Photochem Photobiol 1987, V46, P837
(11) Fingar, V; Cancer Res 1992, V52, P4914 HCAPLUS
(12) Fisher, A; Lasers Surg Med 1995, V17, P2 MEDLINE
(13) Foster, T; Br J Cancer 1996, V73, P933 HCAPLUS
(14) Freeman, D; Photochem Photobiol 2001, V74, P206 HCAPLUS
(15) Gomer, C; Photochem Photobiol 1991, V54, P1093 HCAPLUS
(16) Grossweiner, L; J Photochem Photobiol B: Biol 1997, V38, P258 HCAPLUS
(17) Henderson, B; Photochem Photobiol 1992, V55, P145 HCAPLUS
(18) Hilf, R; Photodynamic Therapy Basic Principles and Clinical Applications 1992, P47 HCAPLUS
(19) Kamuhabwa, A; Photochem Photobiol 2001, V74, P126 HCAPLUS
(20) Keisari, Y; J Immunol Methods 1992, V146, P155 HCAPLUS
(21) Kostenich, G; J Photochem Photobiol B: Biol 1993, V17, P187 HCAPLUS
(22) Lavic, G; Br J Cancer 1999, V79, P423
(23) Moan, J; Photochem Photobiol 1992, V55, P931 HCAPLUS
(24) Morton, C; Br J Dermatol 2000, V143, P767 MEDLINE
(25) Nelson, J; J Natl Cancer Inst 1988, V80, P1599 MEDLINE
(26) Ochsner, M; J Photochem Photobiol B: Biol 1997, V39, P1 HCAPLUS
(27) Schuitmaker, J; J Photochem Photobiol B: Biol 1996, V34, P3 HCAPLUS
(28) Star, W; Cancer Res 1986, V46, P2532 MEDLINE
(29) Tromberg, B; Photochem Photobiol 1990, V52, P375 HCAPLUS

IT **548-04-9**, **Hypericin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(wavelength-dependent properties of **photodynamic** therapy with **hypericin** in colon carcinoma)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:53799 HCAPLUS
DN 137:105823
ED Entered STN: 20 Jan 2002
TI Effects of **photodynamic** therapy with **hypericin** in mice bearing highly invasive solid tumors
AU Blank, Michael; **Lavie, Gad**; Mandel, Mathilda; Keisari, Yona
CS Department of Human Microbiology, Sackler School of Medicine, Tel Aviv University, Tel Aviv-Jaffa, 69978, Israel
SO Oncology Research (2001), Volume Date 2000, 12(9/10), 409-418
CODEN: ONREE8; ISSN: 0965-0407
PB Cognizant Communication Corp.
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
AB The tumoricidal properties of **photodynamic** therapy (PDT) with

hypericin (HY) were evaluated in a highly metastatic adenocarcinoma (DA3Hi) and anaplastic squamous cell carcinoma (SQ2) tumors in vivo. **Photosensitization** of the tumor site with **hypericin** (HY-PDT) reduced primary tumor development and significantly prolonged the survival of tumor-bearing (TB) mice. Of these two tumors, the squamous cell carcinoma emerged as more sensitive to HY-PDT compared with DA3Hi adenocarcinoma both in vitro and in vivo. HY-PDT caused extensive tumor necrosis that was followed by local, intratumoral, and systemic inflammatory reactions. Analyses of cytokine mRNA profiles reveal increases in mRNA levels of expression confined to inflammation-related cytokines both within the tumor and also systemically (measured in spleens). However, there was no evidence for any HY-PDT-induced antitumoral immune reactions. Our results suggest that PDT with **hypericin** can be considered as a supplementary treatment in the management of some invasive and metastatic cancers such as squamous carcinoma and similar tumors.

ST **hypericin** PDT invasive solid neoplasm cytokine; adenocarcinoma squamous carcinoma metastasis **hypericin photosensitizer** PDT

IT Mammary gland, neoplasm
(adenocarcinoma, metastasis; **hypericin** PDT effect on highly invasive solid tumors)

IT Antitumor agents
Photodynamic therapy
Photosensitizers (pharmaceutical)
(**hypericin** PDT effect on highly invasive solid tumors)

IT Interleukin 12
Interleukin 1β
Interleukin 2
Interleukin 4
Interleukin 6
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**hypericin** PDT effect on highly invasive solid tumors)

IT Lung, neoplasm
(metastasis; **hypericin** PDT effect on highly invasive solid tumors)

IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proinflammatory; **hypericin** PDT effect on highly invasive solid tumors)

IT Neoplasm
(solid; **hypericin** PDT effect on highly invasive solid tumors)

IT Carcinoma
(squamous cell, metastasis; **hypericin** PDT effect on highly invasive solid tumors)

IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-; **hypericin** PDT effect on highly invasive solid tumors)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; **hypericin** PDT effect on highly invasive solid tumors)

IT 83869-56-1, Gm-csf
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**hypericin** PDT effect on highly invasive solid tumors)

IT **548-04-9, Hypericin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hypericin** PDT effect on highly invasive solid tumors)

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD

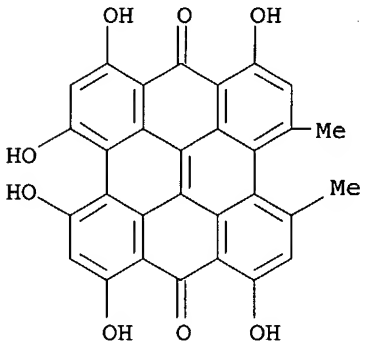
RE

(1) Diwu, Z; Free Radic Biol Med 1993, V14, P209 HCAPLUS
(2) Evans, S; J Natl Cancer Inst 1990, V82, P34 MEDLINE
(3) Hadjur, C; J Photochem Photobiol B Biol 1994, V26, P67 HCAPLUS
(4) Hadjur, C; J Photochem Photobiol B Biol 1995, V27, P139 HCAPLUS
(5) Henderson, B; Radiat Res 1986, V108, P196 HCAPLUS
(6) Katz, B; Int J Cancer 1994, V59, P684 HCAPLUS
(7) Kessel, D; Photochem Photobiol 1984, V39, P851 HCAPLUS
(8) Khan, S; Eur J Cancer 1993, V29, P1686
(9) Kick, G; Cancer Res 1995, V55, P2373 HCAPLUS
(10) Lavie, G; Br J Cancer 1999, V79, P423 HCAPLUS
(11) Lopez, D; J Natl Cancer Inst 1981, V66, P191 MEDLINE
(12) Moan, J; Photochem Photobiol 1992, V55, P931 HCAPLUS
(13) Momma, T; Cancer Res 1998, V58, P5425 HCAPLUS
(14) Mossmann, T; J Immunol Methods 1983, V65, P55
(15) Nelson, J; Photochem Photobiol 1987, V46, P829 HCAPLUS
(16) Rashid, G; J Immunother 1996, V19, P324 HCAPLUS
(17) Thomas, C; Proc Am Assoc Cancer Res 1992, V33, P500
(18) Vandenbogaerde, A; Phytother Res 1996, V10, P150
(19) Weiner, L; J Chem Soc Perkin Trans 1992, V2, P1439
(20) Weishaupt, K; Cancer Res 1976, V36, P2326 HCAPLUS
(21) Yamamoto, N; Photochem Photobiol 1992, V56, P245 HCAPLUS

IT **548-04-9**, **Hypericin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hypericin** PDT effect on highly invasive solid tumors)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

AN **2001:650207** HCAPLUS

DN **135:340943**

ED Entered STN: 05 Sep 2001

TI Cellular photodestruction induced by **hypericin** in AY-27 rat bladder carcinoma cells

AU Kamuhabwa, Appolinary R.; Agostinis, Patrizia M.; D'Hallewin, Marie-Ange; Baert, Luc; De Witte, Peter A. M.

CS Laboratorium voor Farmaceutische Biologie en Fytofarmacologie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.

SO Photochemistry and Photobiology (2001), 74(2), 126-132
CODEN: PHCBAP; ISSN: 0031-8655

PB American Society for Photobiology

DT Journal

LA English

CC 8-9 (**Radiation** Biochemistry)

AB In a recent clin. study we showed that **hypericin** accumulates

selectively in urothelial lesions following intravesical administration of the compound to patients. In the present study the efficacy of **hypericin** as a photochemotherapeutic tool against urinary bladder carcinoma was investigated using the AY-27 cells (chemical induced rat bladder carcinoma cells). The uptake of **hypericin** by the cells increased by prolonging the incubation time and increasing the extracellular **hypericin** concentration **Photodynamic** treatment of the cells incubated with 0.8 and 1.6 μM **hypericin** concns. resulted in remarkable **cytotoxic** effects the extent of which depended on the fluence rates. Photoactivation of 1.6 μM **hypericin** by 0.5, 1.0 or 2.0 mW/cm2 for 15 min resulted in 3, 30 and 95% of the antiproliferative effect, resp. Increasing the photoactivating light dose from 0.45 to 3.6 J/cm2 resulted in a five-fold increase in **hypericin photodynamic** activity. Irresp. of the fluence rates and irradiation times incubation of the cells with 10 μM **hypericin** induced rapid and extensive cell death in all conditions. The type of cell death (apoptosis or necrosis) induced by photoactivated **hypericin** depended largely on the **hypericin** concentration and the postirradn. time. At lower **hypericin** concns. and shorter postirradn. times apoptosis was the prominent mode of cell death; increasing the **hypericin** concentration and/or prolonging the postirradn. time resulted in increased necrotic cell death. Cell pretreatment with the singlet oxygen **quencher** histidine, but not with the free-radical **quenchers**, significantly protected the cells from photoactivated **hypericin** -induced apoptosis, at least when a relatively low concentration (1.25 μM) was used. This result suggests the involvement of a Type-II **photosensitization** process. However, cells treated with higher **hypericin** concns. (2.5-5 μM) were inadequately protected by histidine. Since **hypericin** is thus shown to be a potent and efficient **photosensitizer**, and since the conditions used were the same as when **hypericin** is used clin. to locate early-stage urothelial carcinoma lesions, **hypericin** may well become very important for the **photodynamic** treatment of superficial bladder carcinoma.

ST **hypericin** bladder carcinoma **photodynamic** therapy mechanism

IT Antitumor agents
(bladder carcinoma; cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT Bladder
(carcinoma, inhibitors; cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT **Photodynamic action**
Photosensitizers (pharmaceutical)
(cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT Apoptosis
Necrosis
(mechanism of cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT **Reactive oxygen species**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mechanism of cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT **548-04-9, Hypericin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT 71-00-1, Histidine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(mechanism of cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

IT 7782-44-7, Oxygen, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(singlet; mechanism of cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

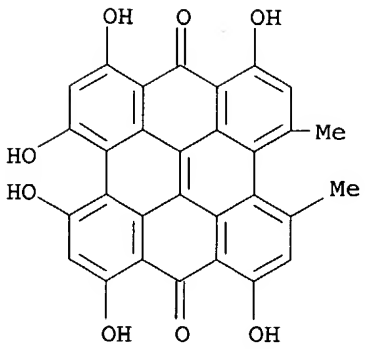
RE

(1) Agarwal, R; Cancer Lett 1991, V56, P125 HCAPLUS
(2) Assefa, Z; J Biol Chem 1999, V274, P8788 HCAPLUS
(3) Dahl, T; Int J Immunopathol Pharmacol 1992, V5, P57
(4) Dougherty, J; Eur J Cancer 1992, V28A, P1742
(5) Dougherty, J; J Natl Cancer Inst 1998, V90, P889
(6) Duran, N; Photochem Photobiol 1986, V43, P677 HCAPLUS
(7) D'Hallewin, M; J Urol 1992, V148, P1152 MEDLINE
(8) D'Hallewin, M; J Urol 2000, V164, P349 MEDLINE
(9) Fridovich, I; Free Radicals in Biology 1976, V1, P239 HCAPLUS
(10) Hadjur, C; J Photochem Photobiol B: Biol 1995, V27, P139 HCAPLUS
(11) Halliwell, B; Cell Biol Int Rep 1978, V2, P113 HCAPLUS
(12) Iinuma, S; Cancer Res 1999, V59, P6164 HCAPLUS
(13) Kamuhabwa, A; Anticancer Res 2000, V20, P2579 HCAPLUS
(14) Kamuhabwa, A; Int J Pharm 1999, V188, P81 HCAPLUS
(15) Kamuhabwa, A; J Photochem Photobiol B: Biol 1999, V53, P110 HCAPLUS
(16) Kriegmair, M; Br J Urol 1996, V77, P667 HCAPLUS
(17) Lavie, G; Med Res Rev 1995, V15, P111 HCAPLUS
(18) Lin, C; Cancer Res 1991, V51, P1109 HCAPLUS
(19) Linde, K; Br Med J 1996, V313, P253 MEDLINE
(20) Luo, Y; Photochem Photobiol 1997, V66, P479 HCAPLUS
(21) Melnikova, V; Cancer Lett 1999, V139, P89 HCAPLUS
(22) Meruelo, D; Proc Natl Acad Sci 1988, V85, P5230 HCAPLUS
(23) Nseyo, U; J Clin Laser Med Surg 1998, V16, P61 MEDLINE
(24) Okpanyi, S; Arzneim Forsch 1990, V40, P851 HCAPLUS
(25) Riesenberg, R; Eur J Cancer 1996, V32A, P328 HCAPLUS
(26) Vandenbogaerde, A; Anticancer Res 1996, V16, P1611
(27) Vandenbogaerde, A; J Photochem Photobiol B: Biol 1998, V45, P87 HCAPLUS
(28) Vantieghem, A; FEBS Lett 1998, V440, P19 HCAPLUS
(29) Weiss, M; Atlas of Genitourinary Tract Disorders 1988, P12.8
(30) Xiao, Z; Br J Cancer 1999, V81, P638 MEDLINE
(31) Xiao, Z; Photochem Photobiol 1998, V67, P573 HCAPLUS

IT **548-04-9, Hypericin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cellular photodestruction induced by **hypericin** in bladder carcinoma cells)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:806080 HCAPLUS
DN 134:143877
ED Entered STN: 16 Nov 2000
TI Characteristics of different **photosensitizers**
AU Kimel, Sol; Orenstein, Arie; **Lavie, Gad**
CS Department of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel
SO Photomedicine in Gynecology and Reproduction (2000), 14-38. Editor(s): Wyss, Pius. Publisher: S. Karger AG, Basel, Switz. CODEN: 69AQFM
DT Conference; General Review
LA English
CC 8-0 (Radiation Biochemistry)
AB A review with 107 refs. is presented regarding the general properties and structure-activity relationships of the major groups of **photosensitizers.** Their advantages are discussed in comparison with Photofrin, a com. porphyrin preparation enriched in tumor-localizing components possessing potent **photodynamic** activity. Some nonporphyrin-based **photosensitizers** that appear to exert direct tumoricidal activity are also surveyed.
ST review **photosensitizer photodynamic** therapy
IT **Photodynamic therapy**
Photosensitizers (pharmaceutical)
(characteristics of different **photosensitizers**)
RE.CNT 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abels, C; J Photochem Photobiol B 1997, V40, P305 HCAPLUS
(2) Agostinis, P; Biochem Biophys Res Commun 1996, V220, P613 HCAPLUS
(3) Agostinis, P; Biochem Pharmacol 1995, V49, P1615 HCAPLUS
(4) Ali, H; Photochem Photobiol 1988, V47, P713 HCAPLUS
(5) Allison, B; Br J Cancer 1994, V69, P833 HCAPLUS
(6) Andrejevic-Blant, S; Br J Cancer 1997, V76, P1021 HCAPLUS
(7) Anker, L; Drugs Future 1995, V20, P511
(8) Aramendia, P; Photochem Photobiol 1986, V44, P555 HCAPLUS
(9) Ben-Hur, E; Photodynamic Therapy: Basic Principles and Clinical Applications 1992, P63 HCAPLUS
(10) Berg, K; Photochem Photobiol 1990, V52, P775 HCAPLUS
(11) Bonnett, R; Biochem J 1989, V261, P277 HCAPLUS
(12) Boyle, R; Photochem Photobiol 1996, V64, P469 HCAPLUS
(13) Braslavsky, S; J Photochem Photobiol B 1997, V40, P191 HCAPLUS
(14) Brault, D; J Photochem Photobiol B 1990, V6, P79 HCAPLUS
(15) Brault, D; J Photochem Photobiol B 1993, V20, P191 HCAPLUS
(16) Chan, W; Cancer Res 1990, V50, P4533 HCAPLUS
(17) Chung, P; Laryngoscope 1994, V104, P1471 HCAPLUS
(18) Cohen, D; Science 1992, V256, P542 HCAPLUS
(19) Degar, S; Virology 1993, V197, P796 HCAPLUS

(20) Dhami, S; Photochem Photobiol 1977, V65, P85
(21) Diwu, Z; Biochem Pharmacol 1994, V47, P373 HCAPLUS
(22) Diwu, Z; Free Radical Biol Med 1993, V14, P209 HCAPLUS
(23) Diwu, Z; Photochem Photobiol 1990, V52, P609 HCAPLUS
(24) Diwu, Z; Photochem Photobiol 1995, V61, P529 HCAPLUS
(25) Dougherty, T; Photochem Photobiol 1993, V58, P895 MEDLINE
(26) Edrei, R; J Porphyrins Phthalocyanines 1998, V2, P191 HCAPLUS
(27) Erdrei, R; J Photochem Photobiol B 1999, V50, P197
(28) Etzlstorfer, C; Monatsh Chem 1993, V124, P751 HCAPLUS
(29) Fields, A; Nature 1988, V333, P278 HCAPLUS
(30) Fingar, V; Cancer Res 1992, V52, P4914 HCAPLUS
(31) Fisher, A; Lasers Surg Med 1995, V17, P2 MEDLINE
(32) Garbo, G; J Photochem Photobiol B 1996, V34, P109 HCAPLUS
(33) Gomer, C; Photochem Photobiol 1991, V54, P1093 HCAPLUS
(34) Gopalakrishna, R; Free Radical Biol Med 1993, V15, P530
(35) Gottfried, V; J Photochem Photobiol B 1995, V30, P115 HCAPLUS
(36) Hadjur, C; J Photochem Photobiol B 1994, V26, P67 HCAPLUS
(37) Hadjur, C; J Photochem Photobiol B 1995, V27, P139 HCAPLUS
(38) Henderson, B; Photochem Photobiol 1992, V55, P145 HCAPLUS
(39) Hilf, R; Photodynamic Therapy: Basic Principles and Clinical Applications 1992, P47 HCAPLUS
(40) Hornung, R; Lasers Surg Med 1997, V20, P443 MEDLINE
(41) Hudson, J; Antiviral Res 1991, V15, P101 HCAPLUS
(42) Jori, G; J Photochem Photobiol B 1996, V36, P87 HCAPLUS
(43) Kennedy, J; J Photochem Photobiol B 1992, V14, P275 HCAPLUS
(44) Kluck, R; Science 1997, V275, P1132 HCAPLUS
(45) Kostenich, G; J Photochem Photobiol B 1991, V11, P307 HCAPLUS
(46) Kostenich, G; J Photochem Photobiol B 1993, V17, P187 HCAPLUS
(47) Kostenich, G; J Photochem Photobiol B 1997, V39, P36 HCAPLUS
(48) Lavie, D; Proc 11th Int Symp Med Chem 1990, P321
(49) Lavie, G; Med Res Rev 1995, V15, P111 HCAPLUS
(50) Lavie, G; Proc Natl Acad Sci USA 1989, V86, P5963 HCAPLUS
(51) Lavie, G; Transfusion 1995, V35, P392 HCAPLUS
(52) Luo, Y; Photochem Photobiol 1997, V66, P479 HCAPLUS
(53) Margaron, P; Photochem Photobiol 1996, V63, P217 HCAPLUS
(54) Maziere, J; J Photochem Photobiol B 1991, V8, P351 HCAPLUS
(55) Meruelo, D; Natural Products as Antiviral Agents 1992, P91 HCAPLUS
(56) Meruelo, D; Proc Natl Acad Sci USA 1988, V85, P5230 HCAPLUS
(57) Moan, J; Photochem Photobiol 1992, V55, P931 HCAPLUS
(58) Morlet, L; J Photochem Photobiol B 1995, V28, P25 HCAPLUS
(59) Nelson, J; J Natl Cancer Inst 1988, V80, P1599 MEDLINE
(60) Noodt, B; Br J Cancer 1996, V74, P22 HCAPLUS
(61) Ochsner, M; J Photochem Photobiol B 1997, V39, P1 HCAPLUS
(62) Orenstein, A; Br J Cancer 1996, V73, P937 HCAPLUS
(63) Orenstein, A; Cancer Lett 1997, V120, P229 HCAPLUS
(64) Paquette, B; Photochem Photobiol 1988, V47, P215 HCAPLUS
(65) Peng, Q; Br J Cancer 1995, V72, P565 HCAPLUS
(66) Peng, Q; Cancer 1997, V79, P2282 HCAPLUS
(67) Peng, Q; Cancer Res 1995, V55, P2620 HCAPLUS
(68) Pottier, R; J Photochem Photobiol B 1990, V8, P1 HCAPLUS
(69) Racinet, H; J Chim Phys 1988, V85, P971 HCAPLUS
(70) Reddi, E; J Photochem Photobiol B 1997, V37, P189 HCAPLUS
(71) Ribo, J; J Chem Soc Chem Commun 1994, P681 HCAPLUS
(72) Richter, A; Photochem Photobiol 1993, V57, P1000 HCAPLUS
(73) Ris, H; Lasers Surg Med 1993, V18, P39
(74) Rosenbach-Belkin, V; Photochem Photobiol 1996, V64, P174 HCAPLUS
(75) Rosenthal, I; Photochem Photobiol 1991, V53, P859 HCAPLUS
(76) Schuitmaker, J; J Photochem Photobiol B 1996, V34, P3 HCAPLUS
(77) Segalla, A; Int J Cancer 1997, V72, P329 HCAPLUS
(78) Sessler, J; Acc Chem Res 1994, V27, P43 HCAPLUS
(79) Sokolov, V; Vopr Onkol 1995, V41, P134 MEDLINE
(80) Spikes, J; J Photochem Photobiol B 1990, V6, P259 HCAPLUS
(81) Spikes, J; J Photochem Photobiol B 1993, V17, P135 HCAPLUS

(82) Star, W; Cancer Res 1986, V46, P2532 MEDLINE
(83) Steiner, R; Geburtshilfe Frauenheilkd 1996, V56, P1 HCAPLUS
(84) Strauss, W; J Photochem Photobiol B 1997, V39, P176 HCAPLUS
(85) Streckyte, G; J Photochem Photobiol B 1993, V18, P259 HCAPLUS
(86) Szeimies, R; J Photochem Photobiol B 1996, V36, P213 HCAPLUS
(87) Takahashi, I; Biochem Biophys Res Commun 1989, V165, P1207 HCAPLUS
(88) Tang, J; Antiviral Res 1990, V13, P313 HCAPLUS
(89) Thomas, C; Photochem Photobiol 1992, V55, P47 HCAPLUS
(90) Thomas, C; Photochem Photobiol 1992, V55, P831 HCAPLUS
(91) Toledano, H; J Photochem Photobiol B 1998, V42, P20 HCAPLUS
(92) Tope, W; Photochem Photobiol 1998, V67, P249 HCAPLUS
(93) Tromberg, B; Photochem Photobiol 1990, V52, P375 HCAPLUS
(94) Utsumi, T; Biochem Pharmacol 1995, V50, P655 HCAPLUS
(95) Van Leengoed, H; Photochem Photobiol 1993, V58, P233 HCAPLUS
(96) van Lier, J; Photodynamic Therapy of Neoplastic Disease 1990, V1, P279
(97) Vandenbogaerde, A; J Photochem Photobiol B 1997, V38, P136 HCAPLUS
(98) Vogel, E; Pure Appl Chem 1990, V62, P557 HCAPLUS
(99) Waluk, J; J Am Chem Soc 1991, V113, P5511 HCAPLUS
(100) Weiner, L; J Chem Soc Perkin Trans 1992, V2, P1439
(101) Winkelman, J; J Photochem Photobiol B 1993, V18, P181 HCAPLUS
(102) Winkelman, J; Photodynamic Therapy of Neoplastic Disease 1990, V2, P29
(103) Yamazaki, T; J Phys Chem 1993, V97, P7870 HCAPLUS
(104) Yang, J; Science 1997, V275, P1129 HCAPLUS
(105) Young, S; Photochem Photobiol 1996, V63, P892 HCAPLUS
(106) Zhang, W; Cancer Lett 1995, V96, P31 HCAPLUS
(107) Zhou, C; J Photochem Photobiol B 1996, V33, P219 HCAPLUS

L81 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:119545 HCAPLUS
DN 132:276024
ED Entered STN: 21 Feb 2000
TI Strategies for evaluation of enveloped virus inactivation in red cell concentrates using **hypericin**
AU Prince, Alfred M.; Pascual, Donna; Meruelo, Daniel; Liebes, Leonard; Mazur, Yehuda; Dubovi, Edward; Mandel, Mathilda; **Lavie, Gad**
CS Lindsley F. Kimball Research Institute of The New York Blood Center, New York, NY, 10021, USA
SO Photochemistry and Photobiology (2000), 71(2), 188-195
CODEN: PHCBAP; ISSN: 0031-8655
PB American Society for Photobiology
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
AB **Photodynamically** induced virus inactivation appears promising in preventing transmission of enveloped virus infections in transfusible blood products. The potential for utilizing **hypericin** as a **photosensitizer** to inactivate key enveloped viruses in packed red cell concs. (PRC) was evaluated. In addition to inactivating effectively ≥106 TCID50 of human immunodeficiency virus (HIV), inactivation of bovine viral diarrhea virus (BVDV) in PRC was used as a model for hepatitis C virus to overcome the deficiency in reliable exptl. systems for hepatitis C virus (HCV) inactivation. BVDV was two orders of magnitude more sensitive to inactivation by **hypericin** than HIV. As part of the virucidal efficacy analyses, the effects of **photosensitization** on hemopoietic cell lines carrying quiescent integrated HIV provirus were studied as models for evaluating virus inactivation in latently infected cells. Phorbol ester-induced virus production by these cells was effectively prevented by **photosensitization** with **hypericin**. A refinement of the illumination conditions, incorporating a monochromatic sodium light source with an emission spectrum coinciding with the absorption peak of **hypericin**, was highly virucidal, however, caused unacceptable levels of hemolysis. Red blood cells could be protected from phototoxic

cellular damage by complexing **hypericin** with human serum albumin (albumin-**hypericin**), but the decrease in hemolysis was at the expense of virucidal efficacy. Thus, excitation of **hypericin** with a fluorescent source appears to be useful potentially for virus inactivation in PRC.

ST **photodynamic photosensitizer hypericin** antiviral erythrocyte

IT Albumins, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complexes, with **hypericin**; **photodynamic photosensitizer hypericin** use for viral inactivation in erythrocyte concs.)

IT Anti-AIDS agents
Antiviral agents
Blood products
Bovine diarrhea virus
Erythrocyte
Hemolysis
Hepatitis C virus
Human immunodeficiency virus 1
Photodynamic action
Photosensitizers (pharmaceutical)
(**photodynamic photosensitizer hypericin** use for viral inactivation in erythrocyte concs.)

IT Albumins, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum, **hypericin** complex; **photodynamic photosensitizer hypericin** use for viral inactivation in erythrocyte concs.)

IT **548-04-9**, **Hypericin 548-04-9D**, **Hypericin**, serum albumin complexes **144788-48-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photodynamic photosensitizer hypericin** use for viral inactivation in erythrocyte concs.)

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD

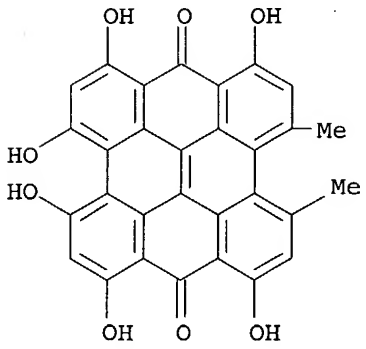
RE

(1) Brown, E; Nucleic Acids Res 1992, V20, P5041 HCAPLUS
(2) Carpenter, S; Photochem Photobiol 1991, V53, P169 HCAPLUS
(3) Choo, Q; Proc Natl Acad Sci USA 1991, V88, P2451 HCAPLUS
(4) Choo, Q; Science 1989, V244, P359 HCAPLUS
(5) Degar, S; Virology 1993, V197, P796 HCAPLUS
(6) Diwu, Z; Free Radicals Biol & Med 1993, V14, P209 HCAPLUS
(7) Hadjur, C; J Photochem Photobiol B Biol 1994, V26, P67 HCAPLUS
(8) Horowitz, B; Blood Coagul Fibrinol 1994, V5(Suppl), P21
(9) Horowitz, B; Transfusion 1991, V31, P102 HCAPLUS
(10) Hudson, J; Antiviral Res 1993, V20, P173 HCAPLUS
(11) Lavie, D; Proceedings of the XIth International Symposium on Medicinal Chemistry 1990, P321
(12) Lavie, G; Br J Cancer 1999, V79, P423 HCAPLUS
(13) Lavie, G; Proc Natl Acad Sci USA 1989, V86, P5963 HCAPLUS
(14) Lavie, G; Transfusion 1995, V35, P392 HCAPLUS
(15) Le, S; Virus Genes 1996, V12, P135 HCAPLUS
(16) Liebes, L; Anal Biochem 1991, V195, P77 HCAPLUS
(17) Lin, L; Blood 1989, V74, P517 HCAPLUS
(18) Margolis-Nunno, H; Transfusion 1996, V36, P743 HCAPLUS
(19) Meruelo, D; Proc Natl Acad Sci USA 1988, V85, P5230 HCAPLUS
(20) Ohba, K; FEBS Lett 1996, V378, P232 HCAPLUS

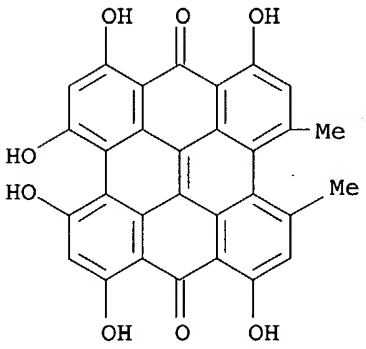
(21) Peter, M; Cell 1990, V61, P591 HCAPLUS
(22) Tabor, E; J Natl Cancer Inst 1992, V84, P86 MEDLINE
(23) Tang, J; Antiviral Res 1990, V13, P313 HCAPLUS
(24) Thomas, C; Photochem Photobiol 1992, V55, P47 HCAPLUS

IT **548-04-9, Hypericin 548-04-9D,**
Hypericin, serum albumin complexes **144788-48-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photodynamic photosensitizer hypericin**
use for viral inactivation in erythrocyte concs.)

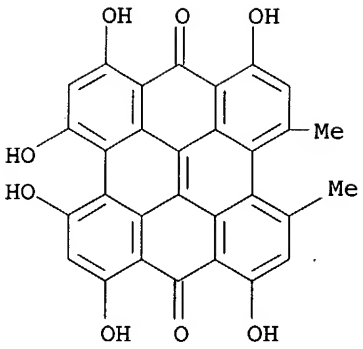
RN 548-04-9 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 548-04-9 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 144788-48-7 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, monosodium salt, stereoisomer (9CI) (CA INDEX NAME)



● Na

L81 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:133039 HCAPLUS
DN 130:334723
ED Entered STN: 02 Mar 1999
TI A **photodynamic** pathway to apoptosis and necrosis induced by dimethyl tetrahydroxyhelianthrone and **hypericin** in leukemic cells: possible relevance to **photodynamic** therapy
AU **Lavie, G.**; Kaplinsky, C.; Toren, A.; Aizman, I.; Meruelo, D.; Mazur, Y.; Mandel, M.
CS Blood Transfusion Center, Sheba Medical Center, Institute of Hematology, Tel-Hashomer, 52621, Israel
SO British Journal of Cancer (1999), 79(3/4), 423-432
CODEN: BJCAAI; ISSN: 0007-0920
PB Churchill Livingstone
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
AB The mechanism of cell death induction by di-Me tetrahydroxyhelianthrone (DTHe), a new second-generation **photodynamic** sensitizer, is analyzed in human leukemic cell lines in comparison with the structurally related **hypericin.** DTHe has a broad range of light spectrum absorption that enables effective utilization of polychromatic light. **Photosensitization** of HL-60 cells with low doses of DTHe (0.65 μM DTHe and 7.2 J cm-2 light energy) induced rapid apoptosis of ≥90% of the cells. At doses ≥2 μM, dying cells assumed morphol. necrosis with perinucleolar condensation of chromatin in HL-60 and K-562 cell lines. Although nuclear fragmentation that is characteristic to apoptosis was prevented, DNA digestion to oligonucleosomes proceeded unhindered. Such incomplete apoptosis was more prevalent with the related analog **hypericin** throughout most doses of **photosensitization.** Despite **hypericin** being a stronger **photosensitizer**, DTHe exhibited advantageous phototoxic properties to tumor cells, initiating apoptosis at concns. about threefold lower than **hypericin.**
Photosensitization of the cells induced dissociation of the nuclear envelope, releasing lamins into the cytosol. DTHe also differed from **hypericin** in effects exerted on the nuclear lamina, causing release of an 86-kDa lamin protein into the cytosol that was unique to DTHe. Within the nucleus, nuclear envelope lamin B underwent covalent polymerization, which did not affect apoptotic nuclear fragmentation at low doses of DTHe. At higher doses, polymerization may have been extensive enough to

prevent nuclear collapse. Hut-78, CD4+ cells were resistant to the **photodynamically** activated apoptotic pathway. Beyond the tolerated levels of **photodynamic** damage, these cells died exclusively via necrosis. Hut-78 cells overexpress Bcl-XL as well as a truncated Bcl-XLtr isoform that could contribute to the observed resistance to apoptosis.

ST helianthrone **hypericin photodynamic** action apoptosis necrosis; leukemia helianthrone **hypericin photodynamic** action

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bax; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bcl-x; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lamins, B; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lamins; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Antitumor agents
(leukemia; **photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT Apoptosis
Necrosis
Photodynamic therapy
Photosensitizers (pharmaceutical)
(**photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

IT **548-04-9**, **Hypericin** 220264-81-3, 10,13-Dimethyl-1,3,4,6-tetrahydroxyhelianthrone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

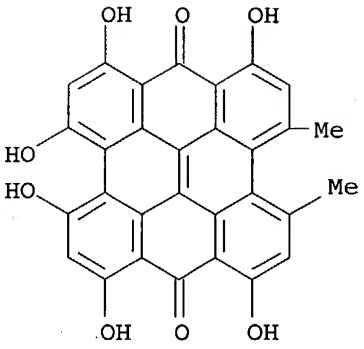
(1) Agostinis, P; Biochem Biophys Res Commun 1996, V220, P613 HCAPLUS
(2) Agostinis, P; Biochem Pharmacol 1995, V49, P1615 HCAPLUS
(3) Anker, L; Drugs Future 1995, V20, P511

(4) Boise, L; Cell 1993, V74, P597 HCAPLUS
(5) Carpenter, S; Photochem Photobiol 1991, V53, P169 HCAPLUS
(6) Chattopadhyay, S; J Photochem 1984, V24, P1 HCAPLUS
(7) Chung, P; Laryngoscope 1994, V104, P1471 HCAPLUS
(8) Degar, S; AIDS Res and Human Retroviruses 1992, V8, P1929 HCAPLUS
(9) Degar, S; Virology 1993, V197, P796 HCAPLUS
(10) Diwu, Z; Free Radical Biol Med 1993, V14, P209 HCAPLUS
(11) Diwu, Z; Photochem Photobiol 1990, V52, P606
(12) Diwu, Z; Photochem Photobiol 1995, V61, P529 HCAPLUS
(13) Dougherty, T; Photochem Photobiol 1983, V38, P377 HCAPLUS
(14) Evans, S; J Natl Cancer Inst 1990, V82, P34 MEDLINE
(15) Gomer, C; Photochem Photobiol 1991, V61, P529
(16) Granville, D; Cell Death Differ 1997, V4, P623 HCAPLUS
(17) Grossweiner, L; The Science of Phototherapy 1994
(18) Hadjur, C; J Photochem Photobiol 1995, V27, P139 HCAPLUS
(19) Hadjur, C; J Photochem Photobiol B Biol 1994, V26, P67 HCAPLUS
(20) Honigsmann, H; Photo Dermatol 1987, V4, P55 MEDLINE
(21) Hudson, J; Antiviral Res 1993, V20, P173 HCAPLUS
(22) Jones, L; J Photochem Photobiol 1996, VB33, P153
(23) Kessel, D; Photochem Photobiol 1984, V39, P851 HCAPLUS
(24) Kick, G; Br J Cancer 1996, V74, P30 HCAPLUS
(25) Kick, G; Cancer Res 1995, V55, P2373 HCAPLUS
(26) Kluck, R; Science 1997, V275, P1132 HCAPLUS
(27) Lavie, D; Trends in Medicinal Chemistry '90. Proceedings of the XIth International Symposium on Medicinal Chemistry 1990, P321
(28) Lavie, G; Proc Natl Acad Sci USA 1989, V86, P5963 HCAPLUS
(29) Li, X; Cancer Res 1994, V54, P4289 HCAPLUS
(30) Lotem, J; Blood 1991, V78, P953 HCAPLUS
(31) Lotem, J; Cell Growth Difference 1995, V6, P647 HCAPLUS
(32) McCaughan, J; Prog Clin Biol Res 1984, V170, P805
(33) Meruelo, D; Proc Natl Acad Sci USA 1988, V85, P5230 HCAPLUS
(34) Miller, G; Photochem Photobiol 1997, V65, P714 HCAPLUS
(35) Mossman, T; J Immunogenet 1983, V21, P235
(36) Murray, N; J Biol Chem 1994, V269, P21385 HCAPLUS
(37) Noodt, B; Br J Cancer 1996, V74, P22 HCAPLUS
(38) Orenstein, A; Lasers Life Sci 1996, V7, P1
(39) Pace, N; Am J Physiol 1942, V136, P650 HCAPLUS
(40) Peter, M; Cell 1990, V61, P591 HCAPLUS
(41) Senthil, V; Biochim Biophys Acta 1992, V1115, P192 HCAPLUS
(42) Takahashi, A; Proc Nat Acad Sci USA 1996, V93, P8395 HCAPLUS
(43) Takahashi, I; Biochem Biophys Res Commun 1989, V165, P1207 HCAPLUS
(44) Tang, J; Antiviral Res 1990, V13, P313 HCAPLUS
(45) Thomas, C; Photochem Photobiol 1992, V55, P47 HCAPLUS
(46) Thomas, C; Photochem Photobiol 1992, V55, P831 HCAPLUS
(47) Weiner, L; J Chem Soc Perkin Trans 1992, V2, P1439
(48) Yang, J; Science 1997, V275, P1129 HCAPLUS
(49) Zhang, W; Cancer Lett 1995, V96, P31 HCAPLUS

IT **548-04-9**, **Hypericin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photodynamic** pathway to apoptosis and necrosis induced by di-Me tetrahydroxyhelianthrone and **hypericin** in leukemic cells)

RN 548-04-9 HCAPLUS

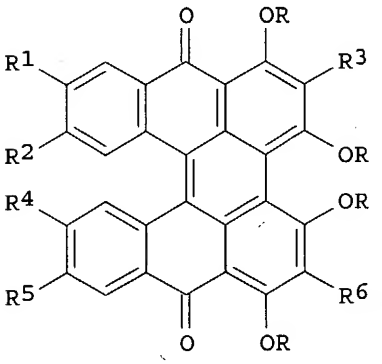
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:113631 HCAPLUS
DN 130:153478
ED Entered STN: 19 Feb 1999
TI Preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivatives in **photodynamic** therapy of tumors
IN Mazur, Yehuda; **Lavie, Gad**
PA Yeda Research and Development Company Ltd., Israel; New York University
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C050-36
ICS C07C069-95; A61K031-12; A61K031-235; A61K041-00
CC 25-28 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9906347	A1	19990211	WO 1998-IL346	19980727
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9883555	A1	19990222	AU 1998-83555	19980727
	EP 1001924	A1	20000524	EP 1998-933874	19980727
	EP 1001924	B1	20030423		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	AT 238264	E	20030515	AT 1998-933874	19980727
	US 6229048	B1	20010508	US 2000-494296	20000131
	~~WO 2001056558~~	A1	20010809	WO 2001-IL91	20010131
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1313459	A1	20030528	EP 2001-902613	20010131
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2003105357 A1 20030605 US 2002-209427 20020730
PRAI IL 1997-121440 A 19970731
WO 1998-IL346 W 19980727
US 2000-494296 A 20000131
WO 2001-IL91 W 20010131
CLASS
PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES
WO 9906347 ICM C07C050-36
ICS C07C069-95; A61K031-12; A61K031-235; A61K041-00
US 2003105357 ECLA A61K031/122; A61K031/136; A61K031/235
OS MARPAT 130:153478
GI



I

AB Use of title compds. (I; R = H, alkyl; R1-R6 = H, OH, Cl, Br, alkyl, alkoxy, alkoxycarbonyl) in the manufacture of pharmaceutical compns. for use in **photodynamic** therapy of tumors is claimed. Thus, 1,3-dihydroxy-6-methylanthraquinone in refluxing HOAc was treated with SnCl2 in concentrate HCl over 2 h followed by stirring at 90° for 2 h to give the anthrone, which was refluxed with pyridine N-oxide and FeSO4.7H2O in pyridine/piperidine to give 10,13-dimethyl-1,3,4,6-tetrahydroxyhelianthrone (DTHe). The latter caused death of HL-60 cells with LD50 = 1 μM at 4.8 J/cm2, approx. 3-fold lower than with **hypericin.**

ST hydroxyhelianthrone prepn **photodynamic** therapy agent anticancer; helianthrone tetrahydroxy prepn **photodynamic** therapy agent anticancer

IT **Photodynamic therapy**
(agents; preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivs. in **photodynamic** therapy of tumors)

IT Antitumor agents
(preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivs. in **photodynamic** therapy of tumors)

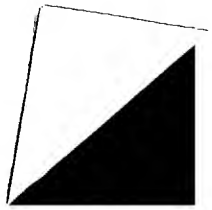
IT 220264-81-3P, 10,13-Dimethyl-1,3,4,6-tetrahydroxyhelianthrone 220264-82-4P 220264-83-5P 220264-84-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivs. in **photodynamic** therapy of tumors)

IT 6219-65-4, 1,3-Dihydroxy-6-methylanthraquinone 220264-88-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivs. in **photodynamic** therapy of tumors)

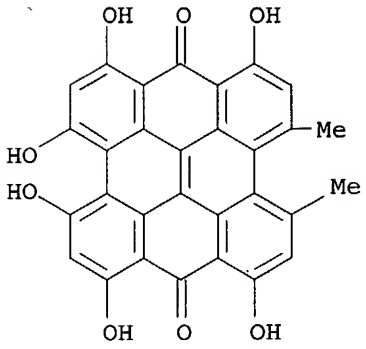
IT 75332-14-8P 220264-85-7P 220264-86-8P 220264-87-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and use of 1,3,4,6-tetrahydroxyhelianthrone and its derivs. in **photodynamic** therapy of tumors)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Kyowa Hakko Kogyo Kk; EP 0390181 A 1990 HCAPLUS
(2) Rodewald, G; Angew Chem (Ancead) 1977, V89(1), P56 HCAPLUS
(3) Univ Iowa Res Found; WO 9414956 A 1994 HCAPLUS
(4) Univ New York; WO 9607731 A 1996 HCAPLUS
(5) Weiner, L; J Chem Soc, Perkin Trans 2 (JCPKBH, 03009580) 1992, 9, P1439 HCAPLUS
(6) Yeda Res & Dev; WO 9427952 A 1994 HCAPLUS

L81 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:119627 HCAPLUS
DN 122:4489
ED Entered STN: 08 Nov 1994
TI **Photosensitization** of the antivirally active **hypericin** complexes with albumin
AU Freeman, D.; Kapinus, E.; Lavie, D.; **Lavie, G.**; Meruelo, D.; Mazur, Y.
CS Dep. Organ. Chem., Weizmann Inst. Sci., Rehovot, Israel
SO Polish Journal of Chemistry (1994), 68(7), 1435-6
CODEN: PJCHDQ; ISSN: 0137-5083
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
AB The **photosensitizing** potential of **hypericin**-albumin complex is examined with respect to its use as an antiviral, especially to HIV virus.
ST **photosensitizing** antiviral **hypericin** albumin
IT **Photodynamic action**
(antiviral; **photosensitizing** antiviral potential of **hypericin**-albumin complex)
IT Albumins, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hypericin** complexes; **photosensitizing** antiviral potential of **hypericin**-albumin complex)
IT **Photosensitizers**
(**photosensitizing** antiviral potential of **hypericin** -albumin complex)
IT Virucides and Virustats
(**photosensitizing**; **photosensitizing** antiviral potential of **hypericin**-albumin complex)
IT Virus, animal
(human immunodeficiency, **photosensitizing** antiviral potential of **hypericin**-albumin complex)
IT **548-04-9D, Hypericin**, albumin complexes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photosensitizing** antiviral potential of **hypericin** -albumin complex)
IT **548-04-9D, Hypericin**, albumin complexes
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**photosensitizing** antiviral potential of **hypericin** -albumin complex)
RN 548-04-9 HCAPLUS

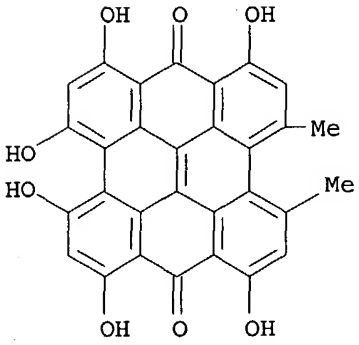


CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:26554 HCAPLUS
DN 120:26554
ED Entered STN: 22 Jan 1994
TI **Photodynamic** inactivation of radiation leukemia virus produced from **hypericin**-treated cells
AU Degar, Steven; **Lavie, Gad**; Meruelo, Daniel
CS Med. Cent., New York Univ., New York, NY, 10016, USA
SO Virology (1993), 197(2), 796-800
CODEN: VIRLAX; ISSN: 0042-6822
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)
Section cross-reference(s): 1
AB **Hypericin** (I) has both in vivo and in vitro antiretroviral activities. To gain further insight into the mechanism(s) by which I exerts its antiretroviral effects, the authors studied Radiation Leukemia virus (RadLV) produced from cells pulse-treated with **hypericin.** The I treatment did not inhibit retroviral production or the proteolytic cleavage of the gag-encoded precursor proteins. I was associated with RadLV particles, and the retrovirions showed an increased d. in sucrose, and the RadLV protein banding patterns were altered. RadLV produced from I-treated cells was rendered noninfectious upon exposure to visible light. The authors' results suggest that RadLV produced from I-treated cells in inactivated by a I-mediated **photodynamic** process.
ST **photodynamic** inactivation radiation leukemia virus **hypericin**; light leukemia inhibition **hypericin**; virucide **hypericin photodynamic** inactivation leukemia light
IT Virucides and Virustats
(**hypericin**, in **photodynamic** inactivation of radiation leukemia virus)
IT **Photosensitizers**
(**hypericin**, of radiation leukemia virus to visible light)
IT Light
(sensitization to, of radiation leukemia virus by **hypericin**)
IT **Phototherapy**
(**chemo-**, with **hypericin** and visible light, of radiation leukemia virus)
IT Neoplasm inhibitors
(leukemia, **photosensitizing**, **hypericin** with visible light)
IT Virus, animal
(radiation leukemia, **photodynamic** inactivation of, from **hypericin**-treated cells)

IT **Photodynamic action**
(therapeutic, of **hypericin**, on radiation leukemia virus with visible light)
IT **548-04-9, Hypericin**
RL: BIOL (Biological study)
(**photodynamic** inactivation of radiation leukemia virus produced from cells treated with)
IT **548-04-9, Hypericin**
RL: BIOL (Biological study)
(**photodynamic** inactivation of radiation leukemia virus produced from cells treated with)
RN 548-04-9 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L81 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1988:504223** HCAPLUS
DN **109:104223**
ED Entered STN: 01 Oct 1988
TI Therapeutic agents with dramatic antiretroviral activity and little toxicity at effective doses: aromatic polycyclic diones **hypericin** and pseudohypericin
AU Meruelo, Daniel; **Lavie, Gad**; Lavie, David
CS Med. Cent., New York Univ., New York, NY, 10016, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1988), 85(14), 5230-4
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
CC 1-5 (Pharmacology)
Section cross-reference(s): 11
AB Two aromatic polycyclic diones **hypericin** and pseudohypericin have potent antiretroviral activity; these substances occur in plants of the Hypericum family. Both compds. are highly effective in preventing virus-induced manifestations that follow infections with a variety of retroviruses in vivo and in vitro. Pseudohypericin and **hypericin** probably interfere with viral infection and/or spread by direct inactivation of the virus or by preventing virus shedding, budding, or assembly at the cell membrane. These compds. have no apparent activity against the transcription, translation, or transport of viral proteins to the cell membrane and also no direct effect on the polymerase. This property distinguishes their mode of action from that of the major antiretrovirus group of nucleoside analogs. **Hypericin** and pseudohypericin have low in vitro cytotoxic activity at concns. sufficient to produce dramatic antiviral effects in murine tissue culture model systems that use radiation leukemia and Friend viruses. Administration of these compds. to mice at the low doses sufficient to prevent

retrovirus-induced disease appears devoid of undesirable side effects. This lack of toxicity at therapeutic doses extends to humans, as these compds. have previously been tested in patients as antidepressants with apparent salutary effects. The observations to date suggest that pseudohypericin and **hypericin** could become therapeutic tools against retrovirus-induced diseases such as acquired immunodeficiency syndrome (AIDS).

ST antiviral **hypericin** pseudohypericin retrovirus toxicity

IT Antigens
RL: BIOL (Biological study)
(expression of, in retrovirus, **hypericin** and pseudohypericin effect on, antiviral mechanism in)

IT Ribonucleic acids, messenger
RL: BIOL (Biological study)
(**hypericin** and pseudohypericin effect on, of retroviruses, antiviral mechanism in)

IT Hypericum triquetrifolium
(**hypericin** and pseudohypericin extraction from)

IT Virus, animal
(Friend leukemia, infection with, treatment of, with **hypericin** and pseudohypericin, mechanism of)

IT Virus, animal
(radiation leukemia, infection with, treatment of, with **hypericin** and pseudohypericin, mechanism of)

IT Virus, animal
(retro-, infection with, treatment of, with **hypericin** and pseudohypericin, mechanism of)

IT Microbicidal and microbiostatic action
(virucidal, of **hypericin** and pseudohypericin, against retroviruses)

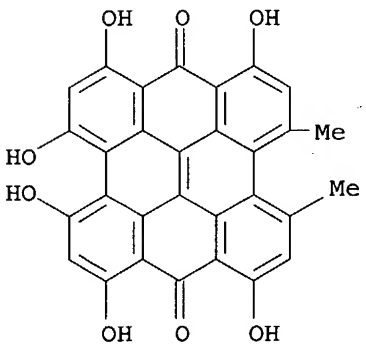
IT **548-04-9**, **Hypericin** 55954-61-5, Pseudohypericin
RL: BIOL (Biological study)
(extraction from **Hypericin** triquetrifolium of and antiretroviral activity and toxicity of)

IT 9068-38-6
RL: BIOL (Biological study)
(**hypericin** and pseudohypericin effect on, of retrovirus, antiviral mechanism in)

IT **548-04-9**, **Hypericin**
RL: BIOL (Biological study)
(extraction from **Hypericin** triquetrifolium of and antiretroviral activity and toxicity of)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



```
=> => fil wpix
FILE 'WPIX' ENTERED AT 15:17:52 ON 19 OCT 2004
COPYRIGHT (C) 2004 THE THOMSON CORPORATION

FILE LAST UPDATED:          15 OCT 2004      <20041015/UP>
MOST RECENT DERWENT UPDATE:     200466        <200466/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
    http://thomsonderwent.com/coverage/latestupdates/           <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/               <<<

>>> NEW! FAST-ALERTING ACCESS TO NEWLY-PUBLISHED PATENT
    DOCUMENTATION NOW AVAILABLE IN DERWENT WORLD PATENTS INDEX
    FIRST VIEW - FILE WPIFV.
    FOR FURTHER DETAILS: http://www.thomsonderwent.com/dwpifv  <<<

>>> NEW DISPLAY FORMAT HITSTR ADDED ALLOWING DISPLAY OF
    HIT STRUCTURES WITHIN THE BIBLIOGRAPHIC DOCUMENT  <<<

=> d all abeq tech abex tot

L97  ANSWER 1 OF 2  WPIX  COPYRIGHT 2004 THE THOMSON CORP on STN
AN   2004-468249 [44]   WPIX
DNC  C2004-175429
TI   Use of quenching photosensitizer molecule for regulating localized
     phototoxicity of effector photosensitizer molecule during photodynamic
     therapy by quenching activity of effector photosensitizer molecule.
DC   B05 P34
IN   LAVIE, G
PA   (LAVI-I) LAVIE G; (UYNY) UNIV NEW YORK STATE
CYC  107
PI   WO 2004047821   A1 20040610 (200444)* EN   41    A61K031-05
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
            LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
            KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
            PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
            VC VN YU ZA ZM ZW
     US 2004176345   A1 20040909 (200459)             A61K031-555    <--
ADT  WO 2004047821 A1 WO 2003-US37743 20031125; US 2004176345 A1
     Provisional US 2002-428677P 20021125, US 2003-720688
     20031125
PRAI US 2002-428677P     20021125; US 2003-720688
     20031125
IC   ICM  A61K031-05; A61K031-555
     ICS  A61N001-30
AB   WO2004047821 A UPAB: 20040712
     NOVELTY - A quenching photosensitizer molecule (B) is used for regulating
     the localized phototoxicity of an effector photosensitizer molecule (A)
     during photodynamic therapy by quenching the activity of (A) in
     neighboring tissues of the tissue targeted for destruction by
     administration prior to administration of (A) and photodynamic therapy.
     The absorption spectrum of (B) falls outside the wavelength range used to
     excite (A).
```

ACTIVITY - Cytostatic; Ophthalmological.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - Used for regulating the localized phototoxicity of (A) during photodynamic therapy, for preventing or reducing the formation of reactive oxygen species and the damage induced by light excited effector photosensitizer molecule in retinal pigmented epithelium during photodynamic therapy of age related macular degeneration, for preventing adverse effect to neighboring tissues during photodynamic occlusion of blood vessels by effector photosensitizer molecule (claimed) and for treating pathological choroidal neovascularization associated with age-related macular degeneration and tumors.
ADVANTAGE - The method protects the tissues adjacent to those targeted for destruction by photosensitization from collateral phototoxic damage. The quenching photosensitizer molecule regulates localized phototoxicity of effector photosensitizer molecule during photodynamic therapy.
Dwg.0/7
FS CPI GMPI
FA AB; DCN
MC CPI: B06-D18; B08-A; B08-D02; B14-H01; **B14-N03**
TECH UPTX: 20040712
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The tissues targeted for destruction is a light-accessible localized tumor or pathological blood vessel emerging from the retinal choroid in the neovascular form of age related muscular degeneration. (A) Comprises is **verteporfin.**
(B) Comprises a **dianthraquinone** or **hypericin**
ABEX UPTX: 20040712
ADMINISTRATION - The quenching photosensitizer molecule is administered at a dosage of 0.01-0.5 mg/kg intravenously 2-72 hours prior to intravenous administration of effector photosensitizer molecule. **Hypericin** is administered at a dosage of 0.01-2 mg/kg intravenously (claimed).

L97 ANSWER 2 OF 2 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN **2003-103675** [09] WPIX
DNC **C2003-026333**
TI Photodynamic therapy treatment to reduce occlusions within the cardiovascular system by utilizing light within the spectral region of 390-610 nm.
DC B05 P34
IN RYCHNOVSKY, S J
PA (RYCH-I) RYCHNOVSKY S J; (MIRA-N) MIRAVANT SYSTEMS INC
CYC 100
PI WO 2002096365 A2 20021205 (200309)* EN 26 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2002183301 A1 20021205 (200315) A61K031-555
AU 2002314846 A1 20021209 (200452) A61K000-00
ADT WO 2002096365 A2 WO 2002-US17069 20020531; US 2002183301 A1 US 2001-871441 20010531; AU 2002314846 A1 AU 2002-314846 20020531
FDT AU 2002314846 A1 Based on WO 2002096365
PRAI US 2001-871441 20010531
IC ICM A61K000-00; A61K031-555
ICS A61K031-353; A61K031-407; A61N001-30
AB WO 200296365 A UPAB: 20030206
NOVELTY - Photodynamic therapy treatment of cardiovascular indications associated with occlusions of a blood vessel involves administering a

photosensitive drug other than psoralen compound, and delivering an intravascular photoactivating light to the blood vessel at an activation wavelength of 390-610 (preferably 440-610) nm such that the molar extinction coefficient of the photosensitive drug at the activation wavelength is at least 1000 l/cm/M.

ACTIVITY - Vulnerary; Vasotropic; Cardiant.

Rat carotid arteries were treated using various wavelengths (442, 458, 514, 532 and 665 nm) of intravascular light and MV6401 (photosensitizer drug). The results at wavelength of 665, 532, 514, 458 and 442 nm, drug dose of 0.1, 2, 2, 2, 1 and 1 micro mol/kg, light dose of 106, 135, 137, 137 and 125 J respectively, and treatment time of 4 hours showed the Maximum Acell. of 0, 60, 70, 57 and 88 %, respectively, and surrounding tissue damage of less than 3, 2, 2, 2 and 1.5 %, respectively.

MECHANISM OF ACTION - None given.

USE - For the treatment of cardiovascular indications associated with occlusions of a blood vessel (claimed); and also for the treatment of other lesions, hyperproliferative cells and occlusive events within the cardiovascular system.

ADVANTAGE - The method eliminates the need for highly selective drug by reducing the average treatment depth relative to that, which results with red/infrared light. Avoids the mutagenic effects associated with excitation using shorter wavelengths and/or psoralens. The method allows the depth of treatment to be controlled in a simple manner by varying the wavelengths of light. The method provides a means for safe treatment by utilizing excitation wavelength for which there is a self-protection benefit in critical surrounding tissues. The treatment provides absorption by hemoglobin significantly limits light propagation in surrounding tissue, thus protecting surrounding tissue from undesired PDT treatment. Scattering of light by tissue is sufficiently high to significantly limit the treatment depth to the target zone. Practical light sources and delivery device can be fabricated for this wavelength range.

Dwg.0/12

FS CPI GMPI

FA AB; DCN

MC CPI: B06-A01; B06-A03; B06-D01; B06-D11; B06-D16; B06-D18; B06-E05; B06-F05; B07-D02; B07-D12; B08-A; B08-D02; B10-B02J; B14-F01; B14-F02; B14-N17B

TECH UPTX: 20030206

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The light is delivered at an activation wavelength of 457 or 458 nm. The time delay between photosensitizer administration and light administration is at most 4 hours.

Preferred Drug: The photosensitizer drug is texaphyrin (preferably lutetium texaphyrin), benzoporphyrin (preferably **visudyne**), xanthene, Rose Bengal, azaporphyrin, phthalocyanine, naturally occurring or synthetic porphyrin (induced by amino-levulinic acid, amino-levulinic ester, amino-levulinic amide, or their derivatives), purpurin, naturally occurring or synthetic chlorin, porphycyanine, isomeric porphyrin, pentaphyrin, sapphyrin, phlorin, naturally occurring or synthetic bacteriochlorin, benzochlorin, **hypericin**, anthraquinone, rhodanol, barbituric acid, expanded porphyrin, dipyrromethene, coumarin, azo, acridine, rhodanine, aazine, tetrazolium, safranine, indocyanine, indigo dye, triazine, pyrrole, naturally occurring or synthetic isobacteriochlorin, naphthalocyanine, phenoxazine, phenothiazine, chalooganapyrylium, triarylmethane, rhodamine, fluorescein, verdin, toluidine, methylene blue, methylene violet, nile blue, nile red, phenazine, pinacyanol, plasmocorinth, or their respective derivatives.

ABEX UPTX: 20030206

ADMINISTRATION - The photosensitizer drug is administered locally or systemically.

=> fil dpci
FILE 'DPCI' ENTERED AT 15:19:54 ON 19 OCT 2004

FILE LAST UPDATED: 13 OCT 2004 <20041013/UP>
PATENTS CITATION INDEX, COVERS 1973 TO DATE

>>> LEARNING FILE LDPCI AVAILABLE <<<

=> d all l98

L98 ANSWER 1 OF 1 DPCI COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2004-468249 [44] DPCI
DNC C2004-175429
TI Use of quenching photosensitizer molecule for regulating localized phototoxicity of effector photosensitizer molecule during photodynamic therapy by quenching activity of effector photosensitizer molecule.
DC B05 P34
IN LAVIE, G
PA (LAVI-I) LAVIE G; (UYNY) UNIV NEW YORK STATE
CYC 107
PI WO 2004047821 A1 20040610 (200444)* EN 41 A61K031-05
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004176345 A1 20040909 (200459) A61K031-555 <--
ADT WO 2004047821 A1 **WO 2003-US37743 20031125**; US 2004176345 A1 **Provisional US 2002-428677P 20021125, US 2003-720688 20031125**
PRAI **US 2002-428677P 20021125; US 2003-720688 20031125**
IC ICM A61K031-05; A61K031-555
ICS A61N001-30
FS CPI GMPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20040901

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	1	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	1	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	0	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	0	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	0	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20040901

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO

WO 2004047821 A1 A US 5047435 A 1988-051265/08
PA: (YEDA) YEDA RES & DEV CO LTD; (UYNY) UNIV NEW YORK STATE
IN: LAVIE, D; REVEL, M; ROTMAN, D; VANDE, VELDE V; VANDEVELDE, V

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:20:04 ON 19 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 19 Oct 2004 VOL 141 ISS 17
FILE LAST UPDATED: 18 Oct 2004 (20041018/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot

L100 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:587584 HCAPLUS
DN 111:187584
ED Entered STN: 25 Nov 1989
TI Antiviral compositions containing aromatic polycyclic diones for treating retrovirus infections
IN Lavie, David; Meruelo, Daniel; **Lavie, Gad**; Revel, Michel; Vande, Velde Vincent; Rotman, Dalia
PA New York University, USA; Yeda Research and Development Ltd.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-05
ICS A61K031-045
CC 1-5 (Pharmacology)
Section cross-reference(s): 11
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8901329	A1	19890223	WO 1988-US2616	19880803
	W: AU, BR, DK, FI, JP				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	AU 8823012	A1	19890309	AU 1988-23012	19880803
	AU 631525	B2	19921203		
	EP 332679	A1	19890920	EP 1988-907908	19880803
	EP 332679	B1	19930616		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
	JP 02501220	T2	19900426	JP 1988-507109	19880803

	JP 2725813	B2	19980311		
	AT 90558	E	19930715	AT 1988-907908	19880803
	ZA 8805838	A	19890426	ZA 1988-5838	19880809
	CA 1329133	A1	19940503	CA 1988-574274	19880810
	US 5047435	A	19910910	US 1989-328767	19890327 <--
	FI 8901665	A	19890407	FI 1989-1665	19890407
	DK 8901674	A	19890609	DK 1989-1674	19890407
PRAI	US 1987-84008		19870810		
	IL 1986-79661		19860808		
	US 1987-82700		19870807		
	EP 1988-907908		19880803		
	WO 1988-US2616		19880803		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 8901329	ICM	A61K031-05
	ICS	A61K031-045

AB Aromatic polycyclic diones, specifically **hypericin** (I) and pseudohypericin (II), are drugs for the treatment of retrovirus infections. I and II were extracted from St. Johnswort (Hypericum triquetrifolium) with Me2CO in a Soxhlet apparatus and separated by silica gel-60 chromatog., using CHCl3-Me2CO-MeOH (75:15:10 and 55:15:10) for elution. Further purification was by flash chromatog. on silica gel-60. II (80 μg/animal, i.p.) administered 24 h after infection decreased the malignant transformational capacity of the Friend leukemia virus in mice, as shown by decreased splenomegaly.

ST retrovirus drug **hypericin** pseudohypericin; Hypericum arom polycyclic dione virucide

IT Hypericum triquetrifolium
(**hypericin** and pseudohypericin from, as virucides)

IT Virucides and Virustats
(**hypericin** and pseudohypericin, against retroviruses)

IT Ketones, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(di-, aryl, polycyclic, virucides, from Hypericum, against retroviruses)

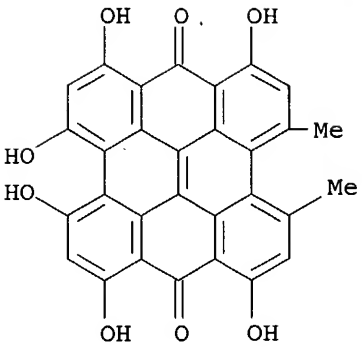
IT Virus, animal
(retro-, infection with, treatment of, **hypericin** and pseudohypericin for)

IT **548-04-9**, **Hypericin** 55954-61-5, Pseudohypericin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(virucide, against retroviruses)

IT **548-04-9**, **Hypericin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(virucide, against retroviruses)

RN 548-04-9 HCAPLUS

CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L100 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:432109 HCAPLUS
DN 109:32109
ED Entered STN: 05 Aug 1988
TI Antiviral pharmaceutical compositions containing **hypericin** or pseudohypericin
IN Lavie, David; Revel, Michel; Rotman, Dalia; Vande Velde, Vincent
PA Yeda Research and Development Co. Ltd., Israel
SO Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K031-12
CC 1-5 (Pharmacology)
FAN.CNT 2

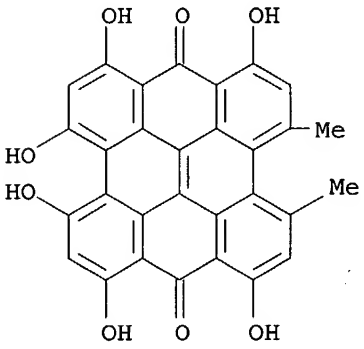
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 256452	A2	19880224	EP 1987-111467	19870807
	EP 256452	A3	19900117		
	EP 256452	B1	19931103		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	IL 79661	A1	19910131	IL 1986-79661	19860808
	US 4898891	A	19900206	US 1987-82700	19870807
	AT 96663	E	19931115	AT 1987-111467	19870807
	ES 2061453	T3	19941216	ES 1987-111467	19870807
	JP 01216922	A2	19890830	JP 1988-40532	19880223
	JP 2502659	B2	19960529		
	US 5047435	A	19910910	US 1989-328767	19890327 <--
	US 5049589	A	19910917	US 1989-452436	19891219
PRAI	IL 1986-79661		19860808		
	EP 1987-111467		19870807		
	US 1987-82700		19870807		
	US 1987-84008		19870810		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 256452	ICM	A61K031-12

AB **Hypericin** (I) and pseudohypericin (II) are antiviral agents effective against vesicular stomatitis (VSV), influenza virus, and herpes simplex virus types I and II. I at 9 μg/mL protected human fibroblasts FS 11 cultures from the cytopathic effect of VSV. II at ≥20 μg/mL inhibited uridine-3H incorporation into VSV RNA to a greater extent than into the cellular RNA in FS 11 cells.
ST virucide **hypericin** pseudohypericin
IT Virucides and Virustats
(**hypericin** and pseudohypericin)
IT Virus, animal

(herpes simplex, infection with, treatment of, with **hypericin** and pseudohypericin)
IT Virus, animal
(influenza, infection with, treatment of, with **hypericin** and pseudohypericin)
IT Virus, animal
(vesicular stomatitis, infection with, treatment of, with **hypericin** and pseudohypericin)
IT Ribonucleic acid formation
(viral, of vesicular stomatitis, pseudohypericin effect on)
IT **548-04-9**, **Hypericin** 55954-61-5, Pseudohypericin
RL: BIOL (Biological study)
(as virucide)
IT **548-04-9**, **Hypericin**
RL: BIOL (Biological study)
(as virucide)
RN 548-04-9 HCAPLUS
CN Phenanthro[1,10,9,8-opqra]perylene-7,14-dione, 1,3,4,6,8,13-hexahydroxy-10,11-dimethyl-, stereoisomer (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



=> => fil medline
FILE 'MEDLINE' ENTERED AT 15:28:40 ON 19 OCT 2004

FILE LAST UPDATED: 17 OCT 2004 (20041017/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l125

L125 ANSWER 1 OF 19 MEDLINE on STN
AN 2003000119 MEDLINE
DN PubMed ID: 12476093
TI Duration of skin photosensitivity and incidence of photosensitivity reactions after administration of **verteporfin.**
AU Houle Jean-Marie; Strong H Andrew
CS QLT Inc., 887 Great Northern Way, Vancouver, British Columbia V5T 4T5, Canada.

SO Retina (Philadelphia, Pa.), **(2002 Dec)** 22 (6) 691-7.
Journal code: 8309919. ISSN: 0275-004X.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200302
ED Entered STN: 20030102
Last Updated on STN: 20030204
Entered Medline: 20030203

AB BACKGROUND: **Verteporfin** (**Visudyne**, Novartis AG) is a light-activated drug that reduces the risk of vision loss in patients with certain types of choroidal neovascularization (CNV). Because photosensitivity can occur with photosensitizers, it is important for ophthalmologists providing **verteporfin** therapy to understand its time course and duration, as well as the incidence of photosensitivity reactions. METHODS: Data were obtained from three sources: 1) the time course of skin photosensitivity in 17 volunteers by measuring erythema/edema over time after **verteporfin**, using red light exposure; 2) the duration of skin photosensitivity in 30 patients with skin cancer by exposing skin to simulated solar light and calculating the daily minimal erythematous dose; and 3) the incidences of photosensitivity reactions as recorded in three phase III trials in patients with CNV secondary to age-related macular degeneration or pathologic myopia who received the regimen of **verteporfin** therapy currently approved by regulatory authorities (infusion of 6 mg/m(2) body surface area). RESULTS: 1) Skin photosensitivity was high at the first timepoint of 1.5 hours after dosing and decreased rapidly thereafter; 2) the duration of skin photosensitivity was dose dependent, ranging from 2.0 to 6.7 days at 6 to 20 mg/m(2), respectively (mean of 2 days at a dose of 6 mg/m(2)); and 3) photosensitivity reactions occurred in only 2.2% of patients in the phase III trials, including two severe events, one secondary to extravasation. All treatment-related reactions in the phase III trials occurred within the first 2 days after dosing, with the exception of two mild reactions and one moderate reaction that occurred 3 days after treatment. CONCLUSIONS: **Verteporfin** is associated with short-lived photosensitivity and a low incidence of photosensitivity reactions in clinical trials, most of which could probably have been avoided by adherence to protocol instructions for skin protection.

CT Check Tags: Comparative Study; Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Choroidal Neovascularization: DT, drug therapy
Choroidal Neovascularization: ET, etiology
Dermatitis, Photoallergic: CL, classification
Dermatitis, Photoallergic: EP, epidemiology
*Dermatitis, Photoallergic: ET, etiology
Incidence
Macular Degeneration: CO, complications
Middle Aged
Myopia: CO, complications
***Photochemotherapy: AE, adverse effects**
Photosensitizing Agents: AD, administration & dosage
***Photosensitizing Agents: AE, adverse effects**
Porphyrins: AD, administration & dosage
***Porphyrins: AE, adverse effects**
*Skin: DE, drug effects
Skin Neoplasms: DT, drug therapy
Skin Neoplasms: PA, pathology

Time Factors
RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 2 OF 19 MEDLINE on STN
AN 2002708440 MEDLINE
DN PubMed ID: 12470762
TI **Photodynamic therapy** using **verteporfin** -induced minimal change nephrotic syndrome.
AU Kang Shin W; Kang Shin J; Kim Hyun O; Nam Eun S; Lee Jin H; Koh Hyoung J
CS Department of Internal Medicine, Institute of Kidney Disease, Yonsei University College of Medicine, Sodaemun-gu, Seoul, South Korea.
SO American journal of ophthalmology, **(2002 Dec)** 134 (6) 907-8.
Journal code: 0370500. ISSN: 0002-9394.
CY United States
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200301
ED Entered STN: 20021217
Last Updated on STN: 20030103
Entered Medline: 20030102
AB PURPOSE: To report a case of minimal change nephrotic syndrome (MCNS) after **photodynamic therapy** using **verteporfin** . DESIGN: Interventional case report. METHODS: After four cycles of **photodynamic therapy**, general weakness with generalized edema developed in an otherwise healthy 66-year-old woman, resulting in dyspnea and ascites. Urinalysis showed heavy proteinuria (4+) with decreased serum total protein and albumin, and increased total cholesterol levels, suggesting nephrotic syndrome. Renal biopsy and pathologic diagnosis were performed. RESULTS: Renal biopsy revealed normal glomeruli and tubulointerstitium by light microscopy, with no immunoglobin or complement deposition. Transmission electron microscopy showed diffuse effacement of the foot processes of visceral epithelial cells, which is the characteristic finding of minimal change nephrotic syndrome. CONCLUSIONS: We herein report a case of minimal change nephrotic syndrome after **photodynamic therapy** using **verteporfin** .
CT Check Tags: Female; Human
Aged
Biopsy
Blood Proteins: ME, metabolism
Cholesterol: BL, blood
Choroidal Neovascularization: DI, diagnosis
Choroidal Neovascularization: DT, drug therapy
Fluorescein Angiography
Kidney: PA, pathology
*Nephrosis, Lipoid: CI, chemically induced
Nephrosis, Lipoid: DI, diagnosis
***Photochemotherapy: AE, adverse effects**
***Photosensitizing Agents: AE, adverse effects**
***Porphyrins: AE, adverse effects**
Proteinuria: DI, diagnosis
RN **129497-78-5 (verteporfin)**; 57-88-5 (Cholesterol)
CN 0 (Blood Proteins); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 3 OF 19 MEDLINE on STN
AN 2002683815 MEDLINE
DN PubMed ID: 12441743
TI Hot spots after **photodynamic therapy** for choroidal neovascularization in age-related macular degeneration.
AU Battaglia Parodi Maurizio; Da Pozzo Stefano

CS Eye Clinic, University of Trieste, Italy.. maubp@yahoo.com
SO Retina (Philadelphia, Pa.), **(2002 Oct)** 22 (5) 671-3.
Journal code: 8309919. ISSN: 0275-004X.
CY United States
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20021123
Last Updated on STN: 20030107
Entered Medline: 20030106
CT Check Tags: Female; Human
Aged
Aged, 80 and over
Choroid: BS, blood supply
***Choroidal Neovascularization: DT, drug therapy**
Choroidal Neovascularization: ET, etiology
Dyes: DU, diagnostic use
Fluorescein Angiography
Indocyanine Green: DU, diagnostic use
***Macular Degeneration: CO, complications**
***Photochemotherapy: AE, adverse effects**
***Photosensitizing Agents: AE, adverse effects**
***Porphyrins: AE, adverse effects**
*Postoperative Complications: CI, chemically induced
Postoperative Complications: DI, diagnosis
Postoperative Complications: PP, physiopathology
Vasculitis: CI, chemically induced
Vasculitis: DI, diagnosis
Vasculitis: PP, physiopathology
RN **129497-78-5 (verteporfin)**; 3599-32-4 (Indocyanine Green)
CN 0 (Dyes); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 4 OF 19 MEDLINE on STN
AN 2002683814 MEDLINE
DN PubMed ID: 12441742
TI Retinal pigment epithelial tear weeks following **photodynamic therapy** with **verteporfin** for choroidal neovascularization secondary to pathologic myopia.
AU Srivastava Sunil K; Sternberg Paul Jr
CS Department of Opthalmology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
SO Retina (Philadelphia, Pa.), **(2002 Oct)** 22 (5) 669-71.
Journal code: 8309919. ISSN: 0275-004X.
CY United States
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200301
ED Entered STN: 20021123
Last Updated on STN: 20030107
Entered Medline: 20030106
CT Check Tags: Female; Human
Adult
Choroidal Neovascularization: DI, diagnosis
***Choroidal Neovascularization: DT, drug therapy**
Choroidal Neovascularization: ET, etiology
Fluorescein Angiography
***Myopia: CO, complications**
***Photochemotherapy: AE, adverse effects**
***Photosensitizing Agents: AE, adverse effects**

***Pigment Epithelium of Eye: DE, drug effects**
Pigment Epithelium of Eye: PA, pathology
***Porphyrins: AE, adverse effects**
***Retinal Perforations: CI, chemically induced**
Retinal Perforations: DI, diagnosis
Visual Acuity
RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 5 OF 19 MEDLINE on STN
AN 2002620004 MEDLINE
DN PubMed ID: 12365909
TI **Verteporfin** therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials--TAP Report number 5.
AU Blumenkranz Mark S; Bressler Neil M; Bressler Susan B; Donati Guy; Fish Gary Edd; Haynes Laurie A; Lewis Hilel; Miller Joan W; Mones Jordi M; Potter Michael J; Pournaras Constantin; Reaves Al; Rosenfeld Philip J; Schachat Andrew P; Schmidt-Erfurth Ursula; Sickenburg Michel; Singerman Lawrence J; Slakter Jason S; Strong Andrew; Vannier Stephane
CS Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group.
SO Archives of ophthalmology, **(2002 Oct)** 120 (10) 1307-14.
Journal code: 7706534. ISSN: 0003-9950.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200210
ED Entered STN: 20021017
Last Updated on STN: 20021030
Entered Medline: 20021029
AB OBJECTIVE: To report vision and safety outcomes from an extension of a 2-year investigation evaluating **verteporfin photodynamic therapy** in patients with age-related macular degeneration with subfoveal choroidal neovascularization (CNV). DESIGN AND SETTING: Open-label extension of selected patients from 2 multicenter, double-masked, placebo-controlled, randomized clinical trials, the Treatment of Age-Related Macular Degeneration With **Photodynamic Therapy** (TAP) Investigation, at 22 ophthalmology practices in Europe and North America. PARTICIPANTS: Patients enrolled in the TAP Investigation and followed up for at least 24 months in whom **verteporfin therapy** to CNV might reduce the risk of further vision loss. METHODS: Before receiving **verteporfin therapy** in the extension, eligible patients signed a written informed consent form accompanied by an oral consent process approved by local institutional review boards. Methods were similar to those described for 1- and 2-year results, with follow-up examinations beyond 2 years continuing at 3-month intervals with a few exceptions, including that extension patients with fluorescein leakage from CNV were to receive open-label **verteporfin therapy** irrespective of their original treatment assignment. RESULTS: Of 402 patients in the **verteporfin** group, 351 (87.3%) completed the month 24 examination; 320 (91.2%) of these enrolled in the extension study. The enrolled participants included 124 (78.0%) of the 159 **verteporfin**-treated patients with lesions composed of predominantly classic CNV at baseline, of whom 105 (84.7%) completed the month 36 examination. **Verteporfin**-treated patients with this lesion composition at baseline who participated in the extension study, with or without a month 36 examination, appeared more likely to have a younger age, better level

of visual acuity, absence of fluorescein leakage from classic CNV, or no progression of classic CNV beyond the baseline boundaries of the lesion at the month 24 examination compared with those who did not enroll in the extension. For the 105 patients with a predominantly classic baseline lesion composition who completed the month 36 examination, an average of 1.3 treatments were given from the month 24 examination up to, but not including, the month 36 examination. A letter score loss in the study eye of at least 15 from baseline for these patients occurred in 39 (37.5%) at the month 24 examination compared with 44 (41.9%) of these patients at the month 36 examination. Visual acuity changed little from the month 24 examination (mean, -1.9 lines) to the month 36 examination (mean, -2.0 lines) for these eyes. **Verteporfin**-treated patients had little change in the mean visual acuity lost and few or no additional instances of infusion-related back pain or photosensitivity reactions from month 24 to month 36. Two patients originally assigned to placebo had acute severe vision decrease within 7 days after **verteporfin** treatment during the extension. One patient originally assigned to **verteporfin** had acute severe vision decrease after **verteporfin** treatment of the fellow eye during the extension. CONCLUSIONS: Vision outcomes for **verteporfin**-treated patients with predominantly classic lesions at baseline remained relatively stable from month 24 to month 36, although only approximately one third of the **verteporfin**-treated patients originally enrolled with this lesion composition had a month 36 examination. From these results, the TAP Study Group identified no safety concerns to preclude repeating **photodynamic therapy** with **verteporfin.** Additional treatment was judged likely to reduce the risk of further vision loss. Caution appears warranted in the absence of comparison with an untreated group during the extension and since not all patients in the TAP Investigation participated in the TAP Extension.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Aged
Aged, 80 and over
***Choroid: BS, blood supply**
Double-Blind Method
Fovea Centralis
***Macular Degeneration: CO, complications**
Macular Degeneration: PP, physiopathology
*Neovascularization, Pathologic: DT, drug therapy
*Neovascularization, Pathologic: ET, etiology
***Photochemotherapy**
Photosensitizing Agents: AE, adverse effects
***Photosensitizing Agents: TU, therapeutic use**
Porphyrins: AE, adverse effects
*Porphyrins: TU, therapeutic use
Safety
Visual Acuity

RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 6 OF 19 MEDLINE on STN
AN 2002391239 MEDLINE
DN PubMed ID: 12140044
TI Adverse reaction characterized by chest pain, shortness of breath, and syncope associated with **verteporfin (visudyne)**.
AU Cahill Mark T; Smith Bradley T; Fekrat Sharon
CS Duke University Eye Center, (M.T.C., B.T.S., S.F.), Durham, North Carolina 27710, USA.
SO American journal of ophthalmology, **(2002 Aug)** 134 (2) 281-2.
Journal code: 0370500. ISSN: 0002-9394.
CY United States
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)

LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200208
ED Entered STN: 20020726
Last Updated on STN: 20020827
Entered Medline: 20020826
AB PURPOSE: To report a serious adverse reaction associated with **verteporfin** infusion. DESIGN: Observational case report. METHODS: Case report of a single individual undergoing **photodynamic therapy** (PDT) with **verteporfin.** RESULTS: A 77-year-old man with long-standing asymptomatic atrial fibrillation, but no known coronary artery disease experienced severe chest and neck pain, shortness of breath, and syncope while undergoing a fourth **photodynamic therapy** (PDT) treatment with **verteporfin.** This infusion had been preceded by three prior infusions; the first two were uneventful, and the third was associated with milder, but similar symptoms. Evaluation demonstrated that the chest pain was noncardiac in origin. CONCLUSION: As **verteporfin** continues to be used around the world, physicians must be alert to the possibility of serious adverse side effects associated with its use.
CT Check Tags: Human; Male
Aged
*Chest Pain: CI, chemically induced
*Dyspnea: CI, chemically induced
Neck Pain: CI, chemically induced
***Photochemotherapy**
***Photosensitizing Agents: AE, adverse effects**
***Porphyrins: AE, adverse effects**
*Syncope: CI, chemically induced
RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 7 OF 19 MEDLINE on STN
AN 2002350942 MEDLINE
DN PubMed ID: 12093647
TI Benefits and complications of **photodynamic therapy** of papillary capillary hemangiomas.
AU Schmidt-Erfurth Ursula M; Kusserow Christine; Barbazetto Irene A; Laqua Horst
CS Department of Ophthalmology, the University Eye Hospital, Ratzeburger Allee 160, 23538 Lubeck, Germany.
SO Ophthalmology, **(2002 Jul)** 109 (7) 1256-66.
Journal code: 7802443. ISSN: 0161-6420.
CY United States
DT (CASE REPORTS)
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020703
Last Updated on STN: 20020719
Entered Medline: 20020718
AB OBJECTIVE: To evaluate the potential benefit and risks of **photodynamic therapy** (PDT) in the treatment of papillary capillary hemangioma. DESIGN: Prospective, noncomparative, interventional case series. PARTICIPANTS: Five patients with solitary capillary hemangioma on the temporal portion of the optic nerve presenting with exudative decompensation and decrease in visual acuity (VA). METHODS: All eyes received a standardized PDT treatment with 6 mg/kg body surface area **verteporfin** and application of 100 J/cm(2) light at 692 nm. One to three PDT courses were performed until resolution of exudation was achieved. A continuous follow-up was provided with documentation 1 week

before and at 4 to 6 weeks, 3 months, and 12 months after the last treatment application. MAIN OUTCOME MEASURES: Functional parameters included best-refracted VA (Early Treatment Diabetic Retinopathy Study), and central scanning laser ophthalmoscope (SLO) scotometry and peripheral (automated perimetry) visual fields; anatomic parameters were presence of retinal edema or serous detachment (ophthalmoscopy) and tumor size (ultrasonography). RESULTS: Pretreatment VA levels ranged from 20/40 to 20/800; posttreatment levels ranged from 20/64 to 20/2000. Tumor regression with resolution of macular exudate and serous retinal detachment was obtained in all eyes. A decline in VA of 1, 3, and 10 lines, respectively, was documented in three patients. Complications included transient decompensation of vascular permeability, occlusion of retinal vessels, and ischemia of the optic nerve. CONCLUSIONS: PDT is successful in reducing tumor size and exudative activity. Vaso-occlusive effects at the level of the retina and optic nerve compromise the functional benefit. Parameters proven safe in choroidal neovascularization may be inappropriate in retinal capillary lesions of the optic nerve.

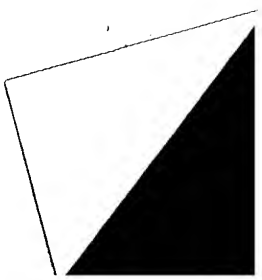
CT Check Tags: Female; Human; Male
Adult
Capillary Permeability: DE, drug effects
Fluorescein Angiography
Fundus Oculi
*Hemangioma, Capillary: DT, drug therapy
Hemangioma, Capillary: PA, pathology
Middle Aged
Ophthalmoscopy
***Optic Disk: BS, blood supply**
***Optic Nerve Neoplasms: DT, drug therapy**
Optic Nerve Neoplasms: PA, pathology
Optic Neuropathy, Ischemic: CI, chemically induced
***Photochemotherapy**
Photochemotherapy: AE, adverse effects
Photosensitizing Agents: AE, adverse effects
***Photosensitizing Agents: TU, therapeutic use**
Porphyrins: AE, adverse effects
*Porphyrins: TU, therapeutic use
Prospective Studies
Retinal Artery Occlusion: CI, chemically induced
Retinal Vein Occlusion: CI, chemically induced
Visual Acuity
Visual Fields

RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 8 OF 19 MEDLINE on STN
AN 2002106647 MEDLINE
DN PubMed ID: 11812424
TI **Verteporfin** infusion-associated pain.
AU Borodoker Natalie; Spaide Richard F; Maranan Leandro; Murray Jane; Freund K Bailey; Slakter Jason S; Sorenson John A; Yannuzzi Lawrence A; Guyer David R; Fisher Yale L
CS Vitreous-Retina-Macula Consultants of New York, and the LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, New York 10021, USA.
SO American journal of ophthalmology, **(2002 Feb)** 133 (2) 211-4.
Journal code: 0370500. ISSN: 0002-9394.
CY United States
DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals

EM 200202
ED Entered STN: 20020213
Last Updated on STN: 20020220
Entered Medline: 20020219
AB PURPOSE: To determine if oral hydration decreases the incidence of **verteporfin** infusion-associated pain and to find out if other factors play a role in predisposing to this undesired complication. METHODS: Nonrandomized clinical trial. We prospectively examined 250 consecutive patients who have been diagnosed with subfoveal choroidal neovascularization secondary to age-related macular degeneration and received **photodynamic therapy** using **verteporfin.** One hundred twenty-five patients were assigned to receive 500 ml of water orally administered 30 minutes before beginning the **verteporfin** infusion, and the remaining 125 consecutive patients were used as controls. Historical and clinical factors in these patients were evaluated for their association with the presence of **verteporfin** infusion-associated pain. RESULTS: Out of 125 patients receiving water before treatment 12 (9.6%) experienced **verteporfin** infusion-associated pain. Among the 125 patients who did not get hydration before **therapy** 12(9.6%) experienced **verteporfin** infusion-associated pain. There was no statistical difference between the incidence of pain in the two groups (P = 1.0). No statistically significant association was evidenced between the presence of pain and participant's baseline characteristics, except for pain on previous administration of **verteporfin** (P < .001). Out of 250 total patients 24 (9.6%) developed **verteporfin** infusion-associated pain. Back pain was the most common and occurred in 21 (8.4%) patients, but other sites included leg, groin, chest, buttock, arm, and shoulder pain concurrently or independently. All patients had resolution of their pain, including chest pain, on cessation of the infusion. CONCLUSIONS: **Verteporfin** infusion-associated pain may be more common than has been previously reported and is not limited to the back area. It appears to be an idiosyncratic reaction to the drug. It does not seem to be prevented by oral hydration before infusion of **verteporfin**, and no baseline characteristics, other than a history of pain on previous infusion, seem to be predictive of **verteporfin** infusion-associated pain.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Administration, Oral
Aged
Aged, 80 and over
*Back Pain: CI, chemically induced
Back Pain: PC, prevention & control
Choroidal Neovascularization: DT, drug therapy
Choroidal Neovascularization: ET, etiology
Fluid Therapy
Infusions, Intravenous
Macular Degeneration: CO, complications
Photochemotherapy
Photosensitizing Agents: AD, administration & dosage
***Photosensitizing Agents: AE, adverse effects**
Porphyrins: AD, administration & dosage
***Porphyrins: AE, adverse effects**
Prospective Studies
Water: AD, administration & dosage
RN **129497-78-5 (verteporfin)**; 7732-18-5 (Water)
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 9 OF 19 MEDLINE on STN
AN 2002066415 MEDLINE
DN PubMed ID: 11793628
TI Verteporfin for age-related macular degeneration.
AU Messmer K J; Abel S R



CS Richard L Roudebush Veterans Affairs Medical Center, Indianapolis, IN, USA.
SO Annals of pharmacotherapy, **(2001 Dec)** 35 (12) 1593-8. Ref: 15
Journal code: 9203131. ISSN: 1060-0280.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200206
ED Entered STN: 20020125
Last Updated on STN: 20020612
Entered Medline: 20020611
AB OBJECTIVE: To review the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, drug-drug interactions, and the **therapeutic** issues concerning the use of verteporfin in patients with age-related macular degeneration (AMD). DATA SOURCES: Published articles and abstracts in English were identified by MEDLINE (1990-August 2000) searches using the search terms verteporfin, treatment of age-related macular degeneration, and **photodynamic therapy** (PDT). Additional references were identified from the bibliographies of the retrieved articles. Data were also obtained from approved product labeling. DATA EXTRACTION: The literature was assessed for adequate description of patients, methodology, and outcomes. DATA SYNTHESIS: Verteporfin is a synthetic benzoporphyrin derivative and a cytotoxic photosensitizing agent, which is one component of PDT. PDT involves administration of verteporfin for injection and nonthermal red light at a wavelength of 689 nm. It is metabolized, to a small extent, to its diacid metabolite by liver and plasma esterases. Information concerning drug interactions is limited. In clinical trials, verteporfin was effective in patients with wet AMD as demonstrated in standard visual acuity scores. Adverse events were related to injection site reactions and visual disturbances. CONCLUSIONS: Verteporfin is a welcome alternative to laser photocoagulation, which can result in damage to the retina and lead to visual loss. Although long-term trials have not been performed in humans, results from monkeys indicate possible improvement in vision following PDT with verteporfin.
CT Check Tags: Human
Clinical Trials
***Macular Degeneration: DT, drug therapy**
***Photosensitizing Agents**
Photosensitizing Agents: PK, pharmacokinetics
Photosensitizing Agents: TU, therapeutic use
*Porphyrins
Porphyrins: AE, adverse effects
Porphyrins: PK, pharmacokinetics
Porphyrins: TU, therapeutic use
Treatment Outcome
RN 129497-78-5 (verteporfin)
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 10 OF 19 MEDLINE on STN
AN 2001095070 MEDLINE
DN PubMed ID: 11146745
TI A potentially life-threatening adverse reaction to **verteporfin.**
CM Comment on: Arch Ophthalmol. 1999 Oct;117(10):1329-45. PubMed ID: 10532441
AU Noffke A S; Jampol L M; Weinberg D V; Munana A
SO Archives of ophthalmology, **(2001 Jan)** 119 (1) 143.
Journal code: 7706534. ISSN: 0003-9950.
CY United States
DT (CASE REPORTS)
Commentary

Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20020517
Entered Medline: 20010125
CT Check Tags: Female; Human
Adult
Choroidal Neovascularization: DT, drug therapy
*Epilepsy, Tonic-Clonic: CI, chemically induced
*Heart Arrest: CI, chemically induced
Photochemotherapy
***Photosensitizing Agents: AE, adverse effects**
***Porphyrins: AE, adverse effects**
*Unconsciousness: CI, chemically induced
RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 11 OF 19 MEDLINE on STN
AN 2001048531 MEDLINE
DN PubMed ID: 10945652
TI Cellular distribution and phototoxicity of benzoporphyrin derivative and Photofrin.
AU Rousset N; Vonarx V; Eleouet S; Carre J; Bourre L; Lajat Y; Patrice T
CS Laboratoire de Photobiologie des Cancers, Departement Laser, Nantes, France.
SO Research in experimental medicine. Zeitschrift fur die gesamte experimentelle Medizin einschliesslich experimenteller Chirurgie, **(2000 Jun)** 199 (6) 341-57.
Journal code: 0324736. ISSN: 0300-9130.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001214
AB **Photodynamic therapy** (PDT) induces cell-membrane damage and alterations in cancer-cell adhesiveness, an important parameter in cancer metastasis. These alterations result from cell sensitivity to photosensitizers and the distribution of photosensitizers in cells. The efficacy of photosensitizers depends on their close proximity to targets and thus on their pharmacokinetics at the cellular level. We studied the cellular distribution of photosensitizers with a confocal microspectrofluorimeter by analysing the fluorescence emitted by benzoporphyrin derivative-monoacid ring A (**BPD-MA**) and Photofrin relative to their cell sensitivity. Two cancer cell lines of colonic origin, but with different metastatic properties, were used: PROb (progressive) and REGb (regressive). For **BPD-MA** (1.75 microg/ml), maximal fluorescence intensity (8,300 cts) was reached after 2 h for PROb and after 1 h (4,900 cts) for REGb. For Photofrin (10 microg/ml), maximal fluorescence intensity (467 cts) was reached after 5 h for PROb and after 3 h (404 cts) for REGb. Intracellular studies revealed stronger cytoplasmic than nuclear fluorescence for both BPD and Photofrin. Both of the sensitizers induced a dose-dependent phototoxicity; LD50 with **BPD-MA** was 93.3 ng/ml for PROb and 71.1 ng/ml for REGb, under an irradiation of 10 J/cm2. With Photofrin, LD50 was 1,270 ng/ml for PROb and 1,200 ng/ml for REGb under an irradiation of 25 J/cm2. The photosensitizer effect within PROb and REGb cancer cells was assessed by incorporation kinetics and toxicity-phototoxicity tests. The intracellular concentration of the photosensitive agent was one important

factor in the effectiveness of PDT, but not the only one contributing to the **photodynamic** effect. In conclusion, this study showed that there was a clear difference between sensitizer uptake and phototoxicity, even in cancer cells of the same origin. This could induce cell-killing heterogeneity in clinics.

CT *Adenocarcinoma
Animals
Antineoplastic Agents: PK, pharmacokinetics
*Antineoplastic Agents: TO, toxicity
Cell Nucleus: ME, metabolism
*Colonic Neoplasms
Dihematoporphyrin Ether: PK, pharmacokinetics
***Dihematoporphyrin Ether: TO, toxicity**
Image Processing, Computer-Assisted
Microscopy, Confocal
Microscopy, Fluorescence
Photosensitizing Agents: PK, pharmacokinetics
***Photosensitizing Agents: TO, toxicity**
Phototherapy: AE, adverse effects
Porphyrins: PK, pharmacokinetics
***Porphyrins: TO, toxicity**
Rats
Rats, Inbred Strains
Tumor Cells, Cultured: DE, drug effects
Tumor Cells, Cultured: ME, metabolism

RN 113719-89-4 (benzoporphyrin D); 97067-70-4 (Dihematoporphyrin Ether)
CN 0 (Antineoplastic Agents); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 12 OF 19 MEDLINE on STN
AN 2000459822 MEDLINE
DN PubMed ID: 10980812
TI **Photodynamic therapy** with verteporfin (Visudyne) for macular degeneration.
AU Anonymous
SO Medical letter on drugs and therapeutics, **(2000 Sep 4)** 42 (1086) 81-2.
Journal code: 2985240R. ISSN: 0025-732X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200009
ED Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000928
CT Check Tags: Human
Clinical Trials
Dose-Response Relationship, Drug
Fees, Pharmaceutical
***Macular Degeneration: DT, drug therapy**
***Photochemotherapy**
***Photosensitizing Agents: TU, therapeutic use**
Porphyrins: AE, adverse effects
Porphyrins: EC, economics
*Porphyrins: TU, therapeutic use
RN 129497-78-5 (verteporfin)
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 13 OF 19 MEDLINE on STN
AN 2000216105 MEDLINE
DN PubMed ID: 10755329
TI **Verteporfin.**
AU Scott L J; Goa K L

CS Adis International Limited, Mairangi Bay, Auckland, New Zealand..
demail@adis.co.nz
SO Drugs & aging, **(2000 Feb)** 16 (2) 139-46; discussion 147-8. Ref: 22
Journal code: 9102074. ISSN: 1170-229X.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000602
AB **Verteporfin**, a benzoporphyrin derivative monoacid ring A, is a photosensitising drug for **photodynamic therapy** (PDT) activated by low-intensity, nonheat-generating light of 689nm wavelength. Activation generates cytotoxic oxygen free radicals. The specificity and uptake of **verteporfin** for target cells with a high expression of low density lipoprotein (LDL) receptors, such as tumour and neovascular endothelial cells, is enhanced by the use of a liposomal formulation and its rapid uptake by plasma LDL. **Verteporfin therapy** (at light doses < 150 J/cm) selectively damages neovascular endothelial cells leading to thrombus formation and specific occlusion of choroidal neovascular vessels in subfoveal lesions in patients with age-related macular degeneration (AMD). Repeated applications of **verteporfin therapy** 6 mg/m2 improved or maintained visual acuity in the majority of patients with some classic subfoveal choroidal neovascularisation (CNV) secondary to AMD at 1 year's follow-up in 2 large multicentre, placebo-controlled, double-blind trials. Furthermore. in a subgroup of these patients with predominantly classic CNV secondary to AMD, there was a significantly more marked visual acuity (VA) benefit with 67.3% of **verteporfin**-treated eyes experiencing less than a 15-letter loss of VA versus 39.3% with placebo treatment. Multiple applications of **verteporfin therapy** were well tolerated in patients with subfoveal CNV secondary to AMD. The most common adverse events were visual disturbances, injection site reactions, photosensitivity reactions and infusion-related back pain.
CT Check Tags: Human
Animals
Antineoplastic Agents: AE, adverse effects
Antineoplastic Agents: PK, pharmacokinetics
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
***Photochemotherapy**
Photosensitizing Agents: AE, adverse effects
Photosensitizing Agents: PK, pharmacokinetics
***Photosensitizing Agents: PD, pharmacology**
Photosensitizing Agents: TU, therapeutic use
Porphyrins: AE, adverse effects
Porphyrins: PK, pharmacokinetics
*Porphyrins: PD, pharmacology
Porphyrins: TU, therapeutic use
RN **129497-78-5 (verteporfin)**
CN 0 (Antineoplastic Agents); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 14 OF 19 MEDLINE on STN
AN 1999447074 MEDLINE
DN PubMed ID: 10519585
TI **Verteporfin photodynamic therapy** retreatment of normal retina and choroid in the cynomolgus monkey.
AU Reinke M H; Canakis C; Husain D; Michaud N; Flotte T J; Gragoudas E S;

Miller J W
CS Laser Research Laboratory, Retina Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston 02114, USA.
SO Ophthalmology, **(1999 Oct)** 106 (10) 1915-23.
Journal code: 7802443. ISSN: 0161-6420.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991018
AB OBJECTIVE: This study evaluated the effect of repeated **photodynamic therapy** (PDT) applications on normal primate retina and choroid using an intravenous infusion of liposomal benzoporphyrin derivative (**verteporfin**). DESIGN: This was an experimental study in a primate model. ANIMALS/CONTROLS: Six cynomolgus monkeys were used as experimental subjects and one monkey was used as a control subject. INTERVENTION: Three consecutive PDT treatments at 2-week intervals were applied over the center of the fovea or the optic nerve of each eye. **Verteporfin** was delivered by intravenous infusion at a dose of 6 mg/m2, 12 mg/m2, or 18 mg/m2. Laser irradiation was then applied using a diode laser (689 nm) with light doses and spot sizes kept constant. MAIN OUTCOME MEASURES: Findings were documented by fundus photography, fluorescein angiography, and light and electron microscopy. RESULTS: A cumulative dose response was seen angiographically and histologically with more severe damage to the retina and choroid noted at higher dye doses. **Photodynamic therapy** applied to the macula using the 6-mg/m2 **verteporfin** dose showed recovery of choriocapillaris, with mild retinal pigment epithelium and outer photoreceptor damage at 6 weeks. At this dose, the optic nerve showed few focal sites of axon atrophy and capillary loss. Treatments over the macula using the 12-mg/m2 and 18-mg/m2 doses led to chronic absence of choriocapillaris and photoreceptors at 6 weeks. One of two optic nerves became atrophic after PDT applications using dye doses of 12 mg/m2, and both optic nerves became atrophic in the 18-mg/m2 dye dose group. CONCLUSION: Limited damage to the retina, choroid, and optic nerve was present in primates treated with multiple PDT sessions using 6 mg/m2 **verteporfin** with light doses and the timing of irradiation kept constant. However, PDT using higher dye doses of 12 mg/m2 and 18 mg/m2 led to significant chronic damage to the normal retina, choroid, and optic nerve.
CT Check Tags: Human; Support, Non-U.S. Gov't
Animals
***Choroid: DE, drug effects**
Choroid: PA, pathology
Choroid Diseases: CI, chemically induced
Choroid Diseases: PA, pathology
Fluorescein Angiography
Fundus Oculi
Infusions, Intravenous
Liposomes
Macaca fascicularis
Optic Disk: DE, drug effects
Optic Disk: PA, pathology
Optic Nerve: DE, drug effects
Optic Nerve: PA, pathology
Optic Nerve Diseases: CI, chemically induced
Optic Nerve Diseases: PA, pathology
***Photochemotherapy: AE, adverse effects**
Photography
Photosensitizing Agents: AD, administration & dosage

***Photosensitizing Agents: AE, adverse effects**
Porphyrins: AD, administration & dosage
***Porphyrins: AE, adverse effects**
***Retina: DE, drug effects**
Retina: PA, pathology
Retinal Diseases: CI, chemically induced
Retinal Diseases: PA, pathology
Retreatment
Safety
RN **129497-78-5 (verteporfin)**
CN 0 (Liposomes); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 15 OF 19 MEDLINE on STN
AN 1999012533 MEDLINE
DN PubMed ID: 9796441
TI Skin necrosis due to **photodynamic** action of benzoporphyrin depends on circulating rather than tissue drug levels: implications for control of **photodynamic therapy.**
AU Lin G C; Tsoukas M L; Lee M S; Gonzalez S; Vibhagool C; Anderson R R; Kollias N
CS Wellman Laboratories of Photomedicine, Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston 02114, USA.
NC 2-T32-AR07098-20 (NIAMS)
2-T32-AR07098-21 (NIAMS)
SO Photochemistry and photobiology, **(1998 Oct)** 68 (4) 575-83.
Journal code: 0376425. ISSN: 0031-8655.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981130
AB In an ideal world, **photodynamic therapy** (PDT) of abnormal tissue would reliably spare the surrounding normal tissue. Normal tissue responses set the limits for light and drug dosimetry. The threshold fluence for necrosis (TFN) was measured in normal skin following intravenous infusion with a photosensitizer, benzoporphyrin derivative monoacid ring A (**BPD-MA**) Verteporin as a function of drug dose (0.25-2.0 mg/kg), wavelength of irradiation (458 and 690 nm) and time interval (0-5 h) between drug administration and irradiation. The **BPD-MA** levels were measured in plasma and skin tissue to elucidate the relationship between TFN, drug kinetics and biodistribution. The PDT response of normal skin was highly reproducible. The TFN for 458 and 690 nm wavelengths was nearly identical and the estimated quantum efficiency for skin response was equal at these two wavelengths. Skin phototoxicity, quantified in terms of 1/TFN, closely correlated with the plasma pharmacokinetics rather than the tissue pharmacokinetics and was quadratically dependent on the plasma drug concentration regardless of the administered drug dose or time interval between drug and light exposure. This study strongly suggests that noninvasive measurements of the circulating drug level at the time of light treatment will be important for setting optimal light dosimetry for PDT with liposomal **BPD-MA**, a vascular photosensitizer.
CT Check Tags: Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals
Drug Carriers
Liposomes
Models, Biological
Necrosis
***Photochemotherapy: AE, adverse effects**

***Photochemotherapy: MT, methods**
***Photosensitizing Agents: AE, adverse effects**
Photosensitizing Agents: BL, blood
***Photosensitizing Agents: PK, pharmacokinetics**
***Porphyrins: AE, adverse effects**
Porphyrins: BL, blood
*Porphyrins: PK, pharmacokinetics
Rabbits
Skin: DE, drug effects
Skin: ME, metabolism
*Skin: PA, pathology
Tissue Distribution
RN 113719-89-4 (benzoporphyrin D)
CN 0 (Drug Carriers); 0 (Liposomes); 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 16 OF 19 MEDLINE on STN
AN 1998265031 MEDLINE
DN PubMed ID: 9602321
TI **Photodynamic therapy** of subfoveal choroidal neovascularization: clinical and angiographic examples.
AU Schmidt-Erfurth U; Miller J; Sickenberg M; Bunse A; Laqua H; Gragoudas E; Zografos L; Birngruber R; van den Bergh H; Strong A; Manjuris U; Fsadni M; Lane A M; Piguet B; Bressler N M
CS University Eye Hospital Lubeck, Germany.
SO Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie, **(1998 May)** 236 (5) 365-74.
Journal code: 8205248. ISSN: 0721-832X.
CY GERMANY: Germany, Federal Republic of
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980716
Last Updated on STN: 19980716
Entered Medline: 19980702
AB BACKGROUND: Conventional photocoagulation of subfoveal choroidal neovascularization (CNV) is often accompanied by visual loss due to thermal damage to adjacent retinal structures. **Photodynamic therapy** (PDT) allows vascular occlusion by selective photochemical destruction of vascular endothelial cells only. In a pilot study we evaluated the use of PDT in CNV. METHODS: In a clinical phase I/II trial, patients with subfoveal CNV were treated with PDT. Benzoporphyrin derivative monoacid ring A (BPD) was used as sensitizer at a drug dose of 6 mg/m2 or 12 mg/m2. Irradiation was performed via a diode laser emitting at 690 nm coupled into a slit lamp. Safe and maximum tolerated light doses were defined by dose escalation from 25 to 150 J/cm2. **Photodynamic** effects were documented ophthalmoscopically and angiographically. RESULTS: Sixty-one patients received a single course of BPD-PDT. Preliminary results suggest no damage to retinal structures within the treated area clinically. Retinal perfusion was not altered, while CNV demonstrated immediate absence of fluorescein leakage in the majority of lesions subsequent to PDT. At optimized parameters (6 mg/m2 and 50 J/cm2) complete cessation of leakage from classic CNV occurred in 100% of cases at 1 week and in 50% at week 4. In 70-80% of classic CNV, leakage reappeared at week 12, but markedly less than before treatment. CONCLUSION: PDT allows temporary absence of leakage from CNV with preservation of visual acuity. The long-term prognosis of CNV secondary

to age-related macular degeneration treated with repeated courses of PDT is being evaluated in a phase III trial.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Aged, 80 and over
Capillary Permeability
***Choroid: BS, blood supply**
Fluorescein Angiography
***Fovea Centralis**
Fundus Oculi
Lasers
Middle Aged
*Neovascularization, Pathologic: DT, drug therapy
***Photochemotherapy**
Photosensitizing Agents: AE, adverse effects
***Photosensitizing Agents: TU, therapeutic use**
Pilot Projects
Porphyrins: AE, adverse effects
*Porphyrins: TU, therapeutic use
Prospective Studies
Recurrence
Safety
RN **129497-78-5 (verteporfin)**
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

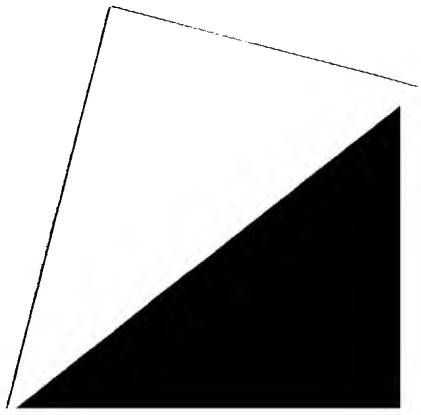
L125 ANSWER 17 OF 19 MEDLINE on STN
AN 97202134 MEDLINE
DN PubMed ID: 9049661
TI Evaluation of the immunotoxicity of benzoporphyrin derivative (**BPD -MA**) in mice.
AU Waterfield J D; Fairhurst M; Waterfield E M; Norbury K C
CS Department of Oral Biology, Faculty of Dentistry, University of British Columbia, Vancouver, Canada.
SO Immunopharmacology and immunotoxicology, **(1997 Feb)** 19 (1) 89-103.
Journal code: 8800150. ISSN: 0892-3973.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
ED Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970508
AB **Photodynamic therapy** has been shown to selectively eliminate activated lymphocytes in a number of experimental situations. These findings have important implications in **therapies** involving selective immunomodulation. In this study we report the effects of intravenous dosing with the photosensitizer benzoporphyrin derivative-monoacid A(BPD) on normal immunological function. **Therapeutic** doses of BPD and light had no effect on natural killer cell activity, the mixed lymphocyte reaction, cell-mediated lympholysis, the primary immune response to sheep red blood cells, or the secondary memory response to T cell-dependent antigens. In non-light treated controls, BPD at concentrations up to 10-fold higher had a limited effect on cell-mediated lympholysis. We conclude that the primary effect of BPD in several **therapeutic** modalities in not due to a generalized suppression of the immune system.
CT Check Tags: Female; Male
Animals
Antibody Formation: DE, drug effects
Cytotoxicity Tests, Immunologic

Erythrocytes: IM, immunology
Immunization, Secondary
Immunologic Memory: DE, drug effects
Killer Cells, Natural: DE, drug effects
Killer Cells, Natural: IM, immunology
Lymphocyte Culture Test, Mixed
Mice
Mice, Inbred A
Mice, Inbred C57BL
Ovalbumin: IM, immunology
Photochemotherapy: AE, adverse effects
***Photosensitizing Agents: TO, toxicity**
***Porphyrins: TO, toxicity**
Sheep
Spleen: CY, cytology
Spleen: IM, immunology
T-Lymphocytes, Cytotoxic: DE, drug effects
T-Lymphocytes, Cytotoxic: IM, immunology
RN 113719-89-4 (benzoporphyrin D); 9006-59-1 (Ovalbumin)
CN 0 (Photosensitizing Agents); 0 (Porphyrins)

L125 ANSWER 18 OF 19 MEDLINE on STN
AN 94134400 MEDLINE
DN PubMed ID: 8302569
TI **Photodynamic therapy** of experimental choroidal melanoma using lipoprotein-delivered benzoporphyrin.
AU Schmidt-Erfurth U; Bauman W; Gragoudas E; Flotte T J; Michaud N A; Birngruber R; Hasan T
CS Wellman Laboratories of Photomedicine, Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston 02114.
SO Ophthalmology, **(1994 Jan)** 101 (1) 89-99.
Journal code: 7802443. ISSN: 0161-6420.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940318
Last Updated on STN: 19940318
Entered Medline: 19940308
AB BACKGROUND: Benzoporphyrin derivative monoacid (BPD) is a new photosensitizer currently undergoing clinical trial for cutaneous malignancies. Compared with the clinically most frequently used sensitizer, Photofrin, BPD may offer higher tumor phototoxicity, better tissue penetration, and absence of significant skin sensitization. Low-density lipoprotein (LDL) carriers heighten efficiency and selectivity of BPD because neovascular and tumor cells express an increased number of LDL receptors. Hence, in addition to the vaso-occlusive effects similar to most other photosensitizers, LDL-BPD also has been shown to cause direct tumor cell damage. METHODS: Benzoporphyrin derivative monoacid was complexed with human LDL and used in photodynamic treatment of choroidal melanomas experimentally induced in eight albino rabbits. Five rabbits served as controls. Three hours after intravenous injection of 2 mg/kg body weight of LDL-BPD, eight tumors were irradiated at 692 nm and 100 J/cm2 via an argon-pumped dye laser coupled into a slit lamp. RESULTS: Angiography and histologic findings showed immediate photothrombosis after disintegration of endothelial membranes. After complete necrosis of tumor cells within 24 hours, a small fibrotic scar slowly developed. No tumor regrowth was noted up to 6 weeks when animals were killed. CONCLUSION: These data suggest that photodynamic treatment with LDL-BPD may be a promising modality for multiple clinical applications, including tumors and neovascularizations II.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.

Animals
***Choroid Neoplasms: DT, drug therapy**
Choroid Neoplasms: PA, pathology
Drug Carriers
Fundus Oculi
Injections, Intravenous
Lasers: TU, therapeutic use
Lipoproteins, LDL
*Melanoma: DT, drug therapy
Melanoma: PA, pathology
Neoplasms, Experimental
***Photochemotherapy**
*Porphyrins: AD, administration & dosage
Porphyrins: AE, adverse effects
Rabbits
***Radiation-Sensitizing Agents: AD, administration & dosage**
Radiation-Sensitizing Agents: AE, adverse effects
RN 113719-89-4 (benzoporphyrin D)
CN 0 (Drug Carriers); 0 (Lipoproteins, LDL); 0 (Porphyrins); 0 (Radiation-Sensitizing Agents)

L125 ANSWER 19 OF 19 MEDLINE on STN
AN 86204770 MEDLINE
DN PubMed ID: 3085038
TI Photosensitizing drugs and their possible role in enhancing ocular toxicity. Parker Heath memorial lecture.
AU Lerman S
NC AGO 1309 (NIA)
EYO 5020 (NEI)
EYO-1575 (NEI)
SO Ophthalmology, **(1986 Mar)** 93 (3) 304-18.
Journal code: 7802443. ISSN: 0161-6420.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198606
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860616
AB During the past decade there has been a considerable resurgence of interest in the photochemical effects of ultraviolet radiation capable of penetrating through the cornea (300-400 nm), on the intraocular tissues. The ocular lens and retina have received the most attention. The last few decades have also witnessed the development of a new therapeutic regimen, namely photosensitizing (phototherapy), in which the patients are given known photosensitizing agents and exposed to nonionizing radiation (ultraviolet, and on occasion, visible radiation). Such therapy has caused some ocular side effects, which in most cases could have been prevented. Drugs that are known photosensitizers and are capable of intraocular penetration through the blood-aqueous and blood-retina barrier are discussed with respect to their known or potential photosensitizing and/or phototoxic effects on intraocular tissues.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Aldehyde Reductase: AI, antagonists & inhibitors
Allopurinol: AE, adverse effects
Doxorubicin: AE, adverse effects
***Eye Diseases: CI, chemically induced**
Fluorescence
Griseofulvin: AE, adverse effects
Lens, Crystalline
Ophthalmology: IS, instrumentation
Ophthalmology: MT, methods



Phenothiazines: AE, adverse effects
*Photochemotherapy: AE, adverse effects
Porphyrins: AE, adverse effects
Psoralens: AE, adverse effects
Retinoids: AE, adverse effects
Tetracycline
RN 126-07-8 (Griseofulvin); 23214-92-8 (Doxorubicin); 315-30-0 (Allopurinol); 60-54-8 (Tetracycline)
CN 0 (Phenothiazines); 0 (Porphyrins); 0 (Psoralens); 0 (Retinoids); EC 1.1.1.21 (Aldehyde Reductase)

=> => fil biosis
FILE 'BIOSIS' ENTERED AT 15:34:15 ON 19 OCT 2004

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 13 October 2004 (20041013/ED)

FILE RELOADED: 19 October 2003.

=> d all tot

L141 ANSWER 1 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2003:518277** BIOSIS
DN **PREV200300512515**
TI "COMPETITIVE QUENCHING" BETWEEN PHOTOSENSITIZERS. A NOVEL CONCEPT IN PROTECTING CELLS FROM **VERTEPORFIN** - INDUCED PHOTOTOXICITY USING **HYPERICIN.**
AU Ron, Y. D. [Reprint Author]; Weinberger, D. [Reprint Author]; Blank, M.; Mandel, M.; Livnat, T.; Lusky, M. [Reprint Author]; Barliya, T.; Orenstein, A.; Meruelo, D.; **Lavie, G.**
CS Ophthalmology, Rabin Medical Center, Petach Tikva, Israel
SO ARVO Annual **Meeting Abstract** Search and Program Planner, (2003) Vol. 2003, pp. **Abstract** No. 1646. cd-rom. Meeting Info.: **Annual Meeting of the Association for Research in Vision and Ophthalmology.** Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 5 Nov 2003
Last Updated on STN: 5 Nov 2003
AB Purpose: Photodynamic therapy (PDT) with **verteporfin** is the accepted treatment for subfoveal choroidal neovascularization in AMD. Time interval of fifteen minutes between I.V administration and the activation by laser irradiation relies on the pharmacokinetics of **verteporfin.** It is impossible to avoid some degree of spillover of the photosensitizer to adjacent retinal pigment epithelium (RPE) which can lead to extensive injury to this tissue. A novel concept termed "competitive quenching" employing a secondary photosensitizer to quench the photosensitizing activity of a primary sensitizer has been developed. We show that competitive quenching can be achieved by using the perihydroxylated **dianthraquinone- hypericin**, to protect RPE cells from the photodynamic effect. Methods: RPE cell cultures and endothelial cell cultures were used. **Hypericin** was added to the cultures. **verteporfin** was added at different time intervals after the **hypericin.** The cultures were irradiated using red light (wavelength of 690nm) to selectively excite **verteporfin.** Cell viability analyses were done. In order to

determine the distribution of **hypericin** among the different layers of the retina and choroid, and its pharmacokinetic properties, animal model was used. Results: Accumulation of **hypericin** in the RPE cell cultures and endothelial cell cultures protected the cells against the photodynamic effect of **verteporfin** and increased their survival substantially. The animal model showed that **hypericin** is bioavailable to the retina and choroid. We show that differnet concentration of **hypericin** can be found in the retina, RPE and choroid 15 minutes, 2,4,6,8 hours following I.V administration. Conclusions: We show here, in vitro, that high degree of protection from the phototoxicity of **verteporfin** and light can be generated in RPE or other epithelial cells loaded with **hypericin.** We demonstrate in rats that conditions can be achieved in which **hypericin** disperses in the retina and choroid, while **verteporfin** is confined to the intravascular compartment. By that, using the pharmacokinetic properties of **hypericin** to achieve maximum protection of the adjacent RPE cells without interfering in the photodynamic process. "Competitive quenching" with **hypericin** may potentially be developed to protect retinal tissues from **verteporfin**-mediated phototoxicity during photodynamic therapy.

CC **General biology - Symposia, transactions and proceedings 00520**
Pathology - Therapy 12512
Sense organs - Physiology and biochemistry 20004
Nervous system - Physiology and biochemistry 20504
Pharmacology - General 22002
Toxicology - General and methods 22501
Toxicology - Pharmacology 22504

IT Major Concepts
Pharmacology; Sense Organs (Sensory Reception); Toxicology

IT Parts, Structures, & Systems of Organisms
choroid: sensory system; retinal pigment epithelium: nervous system, sensory system

IT Diseases
phototoxicity: toxicity

IT Chemicals & Biochemicals
hypericin: radioprotectorant-drug, pharmacodynamics; photosensitizer; **verteporfin**

IT Miscellaneous Descriptors
cell viability; competitive quenching; cytoprotection

RN **548-04-9 (hypericin)**
129497-78-5 (verteporfin)

L141 ANSWER 2 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2002:561713** BIOSIS
DN **PREV200200561713**
TI Wavelength-dependent properties of photodynamic therapy using **hypericin** in vitro and in an animal model.
AU Blank, Michael; Kostenich, Genady [Reprint author]; **Lavie, Gad**; Kimel, Sol; Keisari, Yona; Orenstein, Arie
CS Advanced Technology Center, Sheba Medical Center, Tel Hashomer, 52621, Israel
genakos@sheba.health.gov.il
SO Photochemistry and Photobiology, (September, 2002) Vol. 76, No. 3, pp. 335-340. print.
CODEN: PHCBAP. ISSN: 0031-8655.
DT Article
LA English
ED Entered STN: 30 Oct 2002
Last Updated on STN: 30 Oct 2002
AB Wavelength effects in photodynamic therapy (PDT) with **hypericin** (HY) were examined in a C26 colon carcinoma model both in vitro and in vivo. Irradiation of HY-sensitized cells in vitro with either 550 or 590

nm caused the loss of cell viability in a drug- and light-dose-dependent manner. The calculated ratio of HY-based PDT (HY-PDT) efficiencies at these two wavelengths was found to correlate with the numerical ratio of absorbed photons at each wavelength. In vivo irradiation of C26-derived tumors, 6 h after intraperitoneal administration of HY (5 mg/kg), caused extensive vascular damage and tumor necrosis. The depth of tumor necrosis (d) was more pronounced at 590 than at 550 nm and increased when the light dose was raised from 60 to 120 J/cm2. The maximal depths of tumor necrosis (at 120 J/cm2) were 7.5+-1.5 min at 550 nm and 9.9+-0.8 mm at 590 mm. Both values are rather high in view of the limited penetration of green-yellow light into the tissue. Moreover, the depth ratio, d590/d550=1.3 (P<0.001), is smaller than expected considering the 2.2-fold lower HY absorbance and the 1.7-fold lower tissue penetration of radiation at 550 than at 590 nm. This finding indicates that in vivo the depth at which HY-PDT elicits tumor necrosis is not only determined by photophysical considerations (light penetration, number of absorbed photons) but is also influenced significantly by other mechanisms such as vascular effects. Therefore, despite the relatively short-wavelength peaks of absorption, our observations suggest that HY is an effective photodynamic agent that can be useful in the treatment of tumors with depths in the range of 1 cm.

CC Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Mathematical biology and statistical methods 04500
Radiation biology - Radiation and isotope techniques 06504
Pathology - Therapy 12512
Digestive system - Pathology 14006
Cardiovascular system - Heart pathology 14506
Pharmacology - Clinical pharmacology 22005
Pharmacology - Cardiovascular system 22010
Pharmacology - Digestive system 22014
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Pharmacognosy and pharmaceutical botany 54000

IT Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Cell Biology; Gastroenterology (Human Medicine, Medical Sciences); Mathematical Biology (Computational Biology); Methods and Techniques; Oncology (Human Medicine, Medical Sciences); Pharmacognosy (Pharmacology); Radiology (Medical Sciences)

IT Diseases
colon cancer: digestive system disease, neoplastic disease, drug therapy, radiotherapy
Colonic Neoplasms (MeSH)

IT Chemicals & Biochemicals
hypericin: antineoplastic-drug, cardiovascular-drug, gastrointestinal-drug, radiosensitizer-drug, intraperitoneal administration, tumor-necrotizing effect

IT Methods & Equipment
absorbed photon calculation: drug evaluation method, mathematical method, radiologic method; photodynamic therapy: depth ratio, in vitro, in vivo, pharmacological method, radiologic method, therapeutic method, tissue penetration, tumor-necrotizing effect, vascular effects, wavelength-dependent properties

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C26 cell line: colon carcinoma cell
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **548-04-9 (hypericin)**

L141 ANSWER 3 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2001:552886** BIOSIS
DN **PREV200100552886**
TI Effects of photodynamic therapy with **hypericin** in mice bearing highly invasive solid tumors.
AU Blank, Michael; **Lavie, Gad**; Mandel, Mathilda; Keisari, Yona [Reprint author]
CS Department of Human Microbiology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, 69978, Israel
ykeisari@ccsg.tau.ac.il
SO Oncology Research, (2001) Vol. 12, No. 9-10, pp. 409-418. print.
CODEN: ONREE8. ISSN: 0965-0407.
DT Article
LA English
ED Entered STN: 21 Nov 2001
Last Updated on STN: 25 Feb 2002
AB The tumoricidal properties of photodynamic therapy (PDT) with **hypericin** (HY) were evaluated in a highly metastatic adenocarcinoma (DA3Hi) and anaplastic squamous cell carcinoma (SQ2) tumors in vivo. Photosensitization of the tumor site with **hypericin** (HY-PDT) reduced primary tumor development and significantly prolonged the survival of tumor-bearing (TB) mice. Of these two tumors the squamous cell carcinoma emerged as more sensitive to HY-PDT compared with DA3Hi adenocarcinoma both in vitro and in vivo. HY-PDT caused extensive tumor necrosis that was followed by local, intratumoral, and systemic inflammatory reactions. Analyses of cytokine mRNA profiles reveal increases in mRNA levels of expression confined to inflammation-related cytokines both within the tumor and also systemically (measured in spleens). However, there was no evidence for any HY-PDT-induced antitumoral immune reactions. Our results suggest that PDT with **hypericin** can be considered as a supplementary treatment in the management of some invasive and metastatic cancers such as squamous carcinoma and similar tumors.
CC Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Methods and Techniques; Pharmacology; Tumor Biology
IT Diseases
adenocarcinoma: neoplastic disease, metastatic, treatment
Adenocarcinoma (MeSH)
IT Diseases
anaplastic squamous cell carcinoma: neoplastic disease, metastatic, treatment
IT Chemicals & Biochemicals
cytokine mRNA [cytokine messenger RNA]; **hypericin**: antineoplastic-drug
IT Methods & Equipment
photodynamic therapy: therapeutic method
IT Miscellaneous Descriptors
inflammation; tumor necrosis

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
BALB/c mouse: animal model
DA3-Hi cell line: murine adenocarcinoma cells
SQ2 cell line: murine anaplastic squamous cell carcinoma cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **548-04-9 (hypericin)**

L141 ANSWER 4 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **2001:89669** BIOSIS
DN **PREV200100089669**
TI Characteristics of different photosensitizers.
AU Kimel, Sol [Reprint author]; Orenstein, Arie; **Lavie, Gad**
CS Department of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel
SO Wyss, Pius; Tadir, Yona; Tromberg, Bruce J.; Haller, Urs. (2000) pp. 14-38. Photomedicine in gynecology and reproduction. print.
Publisher: S. Karger Publishers Inc., 26 West Avon Road, Farmington, CT, 06085, USA; S. Karger AG, CH-4009, Basel, Switzerland. Series: Photomedicine in gynecology and reproduction.
ISBN: 3-8055-6905-X (cloth).
DT Book
Book; (Book Chapter)
LA English
ED Entered STN: 14 Feb 2001
Last Updated on STN: 12 Feb 2002
CC Radiation biology - General 06502
Biochemistry studies - General 10060
Pathology - Therapy 12512
Pharmacology - General 22002
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Radiation Biology; Tumor Biology
IT Diseases
cancer: neoplastic disease
Neoplasms (MeSH)
IT Chemicals & Biochemicals
cercosporin: photosensitizer; hematoporphyrin derivative; **hypericin**: photosensitizer, polycyclic aromatic ketone; hypocrellin: photosensitizer; photosensitizer; phthalocyanine: photosensitizer; porphycene: photosensitizer
IT Methods & Equipment
photodynamic therapy [photochemotherapy]: radiologic method, therapeutic method
IT Miscellaneous Descriptors
Book Chapter
RN 35082-49-6 (cercosporin)
548-04-9 (hypericin)
77029-83-5 (hypocrellin)
574-93-6 (phthalocyanine)
100572-96-1 (porphycene)

L141 ANSWER 5 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **1999:143751** BIOSIS
DN **PREV199900143751**
TI A photodynamic pathway to apoptosis and necrosis induced by dimethyl

tetrahydroxyhelianthrone and **hypericin** in leukaemic cells: Possible relevance to photodynamic therapy.

AU **Lavie, G.** [Reprint author]; Kaplinsky, C.; Toren, A.; Aizman, I.; Meruelo, D.; Mazur, Y.; Mandel, M.
CS Blood Transfusion Cent., Sheba Med. Cent., Tel-Hashomer 52621, Israel

SO British Journal of Cancer, (Feb., 1999) Vol. 79, No. 3-4, pp. 423-432. print.
CODEN: BJCAAI. ISSN: 0007-0920.
DT Article
LA English
ED Entered STN: 31 Mar 1999
Last Updated on STN: 31 Mar 1999

AB The mechanism of cell death induction by dimethyl tetrahydroxyhelianthrone (DTHe), a new second-generation photodynamic sensitizer, is analysed in human leukaemic cell lines in comparison with the structurally related **hypericin.** DTHe has a broad range of light spectrum absorption that enables effective utilization of polychromatic light. Photosensitization of HL-60 cells with low doses of DTHe (0.65 gm DTHe and 7.2 J cm-2 light energy) induced rapid apoptosis of >90% of the cells. At doses >2 muM, dying cells assumed morphological necrosis with perinucleolar condensation of chromatin in HL-60 and K-562 cell lines. Although nuclear fragmentation that is characteristic to apoptosis was prevented, DNA digestion to oligonucleosomes proceeded unhindered. Such incomplete apoptosis was more prevalent with the related analogue **hypericin** throughout most doses of photosensitization. Despite **hypericin** being a stronger photosensitizer, DTHe exhibited advantageous phototoxic properties to tumour cells, initiating apoptosis at concentrations about threefold lower than **hypericin.** Photosensitization of the cells induced dissociation of the nuclear envelope, releasing lamins into the cytosol. DTHe also differed from **hypericin** in effects exerted on the nuclear lamina, causing release of an 86-kDa lamin protein into the cytosol that was unique to DTHe. Within the nucleus, nuclear envelope lamin B underwent covalent polymerization, which did not affect apoptotic nuclear fragmentation at low doses of DTHe. At higher doses, polymerization may have been extensive enough to prevent nuclear collapse. Hut-78, CD4+ cells were resistant to the photodynamically activated apoptotic pathway. Beyond the tolerated levels of photodynamic damage, these cells died exclusively via necrosis. Hut-78 cells overexpress Bcl-XL as well as a truncated Bcl-XLtr isoform that could contribute to the observed resistance to apoptosis.

CC Neoplasms - General 24002
Biochemistry methods - General 10050
Biochemistry studies - General 10060
IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Tumor Biology
IT Diseases
leukemia: blood and lymphatic disease, neoplastic disease
Leukemia (MeSH)
IT Chemicals & Biochemicals
dimethyl tetrahydroxyhelianthrone: photodynamic sensitizer;
hypericin: photodynamic sensitizer; lamins; nuclear envelope; polychromatic light; Bcl-X L
IT Methods & Equipment
photodynamic therapy: therapeutic method
IT Miscellaneous Descriptors
apoptosis; necrosis
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hut-78 cell line

HL-60 cell line
K-562 cell line
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **548-04-9 (hypericin)**
74-84-0 (DIMETHYL)

L141 ANSWER 6 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **1995:135913** BIOSIS
DN **PREV199598150213**
TI The chemical and biological properties of **hypericin**: A compound with a broad spectrum of biological activities.
AU **Lavie, Gad** [Reprint author]; Mazur, Yehuda; Lavie, David; Meruelo, Daniel [Reprint author]
CS Dep. Pathology, NYU Med. Cent., 550 First Avenue, New York, NY 10016, USA
SO Medicinal Research **Reviews**, (1995) Vol. 15, No. 2, pp. 111-119.
CODEN: MRREDD. ISSN: 0198-6325.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 3 Apr 1995
Last Updated on STN: 4 Apr 1995
CC Biochemistry studies - General 10060
Biophysics - Molecular properties and macromolecules 10506
Pathology - Therapy 12512
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Therapeutic agents and therapy 24008
Chemotherapy - Antiviral agents 38506
Plant physiology - Chemical constituents 51522
Pharmacognosy and pharmaceutical botany 54000
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacognosy (Pharmacology); Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
HYPERICIN
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; ANTIVIRAL-DRUG; CHEMICAL PROPERTIES; **HYPERICIN**; PHARMACODYNAMICS; PHOTODYNAMIC PROPERTIES
ORGN Classifier
Guttiferae 26135
Super Taxa
Dicotyledones; Angiospermae; Spermatophyta; Plantae
Organism Name
Hypericum crispum
Hypericum hirsutum
Hypericum perforatum
Taxa Notes
Angiosperms, Dicots, Plants, Spermatophytes, Vascular Plants
RN **548-04-9 (HYPERICIN)**

L141 ANSWER 7 OF 7 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN **1988:421673** BIOSIS
DN **PREV198886084285; BA86:84285**
TI THERAPEUTIC AGENTS WITH DRAMATIC ANTIRETROVIRAL ACTIVITY AND LITTLE TOXICITY AT EFFECTIVE DOSES AROMATIC POLYCYCLIC DIONES **HYPERICIN** AND PSEUDOHYPERICIN.
AU MERUELO D [Reprint author]; **LAVIE G**; LAVIE D
CS DEP PATHOL, KAPLAN CANCER CENT, NEW YORK UNIV MED CENT, 550 FIRST AVE, NEW YORK, NY 10016, USA
SO **Proceedings** of the National Academy of Sciences of the United States of America, (1988) Vol. 85, No. 14, pp. 5230-5234.
CODEN: PNASA6. ISSN: 0027-8424.
DT Article

FS BA
LA ENGLISH
ED Entered STN: 19 Sep 1988
Last Updated on STN: 19 Sep 1988
AB Two aromatic polycyclic diones **hypericin** and pseudohypericin have potent antiretroviral activity; these substances occur in plants of the Hypericum family. Both compounds are highly effective in preventing viral-induced manifestations that follow infections with a variety of retroviruses in vivo and in vitro. Pseudohypericin and **hypericin** probably interfere with viral infection and/or spread by direct inactivation of the virus or by preventing virus shedding, budding, or **assembly** at the cell membrane. These compounds have no apparent activity againts the transcription, translation, or transport of viral proteins to the cell membrane and also no direct effect on the polymerase. This property distinguishes their mode of action from that of the major antiretrovirus group of nucleoside analogues. **Hypericin** and pseudohypericin have low in vitro cytotoxic activity at concentrations sufficient to produce dramatic antiviral effects in murine tissue culture model systems that use radiation leukemia and Friend viruses. Administration of these compounds to mice at the low doses sufficient to prevent retroviral-induced disease appears devoid of undesirable side effects. This lack of toxicity at therapeutic doses extends to humans, as these compounds have been tested in patients as antidepressants with apparent salutary effects. Our observations to date suggest that pseudohypericin and **hypericin** could become therapeutic tools against retroviral-induced diseases such as acquired immunodeficiency syndrome (AIDS).
CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Immunological processes and allergy 22018
Virology - Animal host viruses 33506
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006
Chemotherapy - Antiviral agents 38506
Plant physiology - Chemical constituents 51522
Pharmacognosy and pharmaceutical botany 54000
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Clinical Endocrinology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Infection; Pharmacology
IT Miscellaneous Descriptors
HYPERICUM HUMAN IMMUNOLOGIC-DRUG ANTIVIRAL-DRUG ACQUIRED IMMUNODEFICIENCY SYNDROME
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
ORGN Classifier
Guttiferae 26135
Super Taxa
Dicotyledones; Angiospermae; Spermatophyta; Plantae
Taxa Notes
Angiosperms, Dicots, Plants, Spermatophytes, Vascular Plants
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia

```
     Taxa Notes
        Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN   548-04-9 (HYPERICIN)
     55954-61-5 (PSEUDOHYPERICIN)


=> d his

     (FILE 'HOME' ENTERED AT 13:30:46 ON 19 OCT 2004)
                SET COST OFF

     FILE 'REGISTRY' ENTERED AT 13:31:09 ON 19 OCT 2004
                E VERTEPORFIN/CN
L1               1 S E3
L2               0 S 129497-78-5/CRN
                 E C41H42N4O8/MF
L3              35 S E3 AND NR>=6
L4              26 S L3 AND 11393/RID
L5              24 S L3 AND 11393.1.7/RID
L6              24 S L5 AND 9 13 DIPROPANOIC
L7              13 S L6 AND 18 ETHENYL
L8              10 S L7 AND 3 4 BIS METHOXYCARBONYL
L9              10 S L8 AND 4A 8 14 19 TETRAMETHYL
L10             10 S L9 AND ESTER
L11              3 S L10 AND IDS/CI
L12              3 S L1,L11
                 E DIANTHRAQUINONE/CN
L13              1 S E4
                 E C28H14O4/MF
L14              4 S E3 AND C6-C6-C6/ES AND 6/NR
                 SEL RN
L15              0 S E1-E4/CRN
                 E HYPERICIN/CN
L16              1 S E3
                 SEL RN
L17             34 S E1/CRN
L18             11 S L17 NOT (IDS/CI OR MXS/CI OR COMPD OR WITH)
L19              9 S L18 NOT CONJUGATE

     FILE 'HCAPLUS' ENTERED AT 13:42:38 ON 19 OCT 2004
L20            974 S L14,L16,L19
L21           1148 S HYPERICIN# OR NSC407131 OR NSC()(407313 OR 407 313) OR CYCLOS
L22            291 S BIANTHRAQUINON?
L23             20 S BIANTHRACENE (L) TETRONE
L24            101 S BISANTHRAQUINON? OR PHENANTHRO?(L)PERYLEN?(L)DIONE
L25           1505 S L20-L24
L26            276 S L12
L27            176 S VISUDYNE OR CL318952 OR CL()(318952 OR 318 952) OR BPD MA
L28            175 S VERTEPORFIN?
L29            325 S L26-L28
L30              1 S US20040176345/PN OR (WO2003-US37743 OR US2002-428677# OR US20
                 E LAVIE G/AU
L31             62 S E3,E4
                 E LA VIE G/AU
                 E PHOTODYAN/CT
                 E E5+ALL
L32           7161 S E2,E3,E1+NT
                 E E10+ALL
L33           4257 S E8,E9,E7
                 E E6+ALL
L34           1756 S E3,E6,E7
                 E PHOTOSENSITIZ/CT
L35           2076 S E11
```

```
                E E13+ALL
L36          3391 S E4,E3
                E E16+ALL
L37           959 S E5,E6,E4
                E RADIOPROTECT/CT
                E E8+ALL
L38           827 S E1
                E E2+ALL
L39         11428 S E1+NT
L40            41 S L29 (L) ADV/RL
                E MACULA/CT
                E E11+ALL
L41          1097 S E2
                E EYE, DISEASE/CT
L42          1461 S E45,E46
L43          3666 S E3+OLD,NT,PFT,RT (L) (MACULA? OR DEGENER?)
L44          2415 S E3(L)(MACULA? OR DEGENER?)
                E EYE/CT
L45          2897 S E3+OLD,NT,PFT,RT (L) (MACULA? OR DEGENER?)
L46          2834 S E3 (L) (MACULA? OR DEGENER?)
                E CHOROID/CT
                E E4+ALL
L47           652 S E2
                E RETINAL CHOROID/CT
                E RETINA CHOROID/CT
                E CHOROID/CT
L48           884 S (EYE# OR EYE#(L)DISEASE#)/CW  (L) CHOROID?
                E RETINAL PIGMENT/CT
                E E4+ALL
L49          2520 S E2
L50          2686 S (EYE# OR EYE#(L)DISEASE#)/CW  (L) PIGMENT?(L)EPITHEL?
                E REACTIVE OXYGEN/CT
                E E4+ALL
L51         22520 S E3
L52             8 S L25 AND L29
L53             7 S L52 AND L32-L51
L54             8 S L52,L53
L55             2 S L54 AND (EYE? OR MACULA?(L)DEGENER? OR RETINA? OR CHOROID? OR
L56             1 S L55 NOT RETINAMIDE
L57            34 S L31 AND L25,L29
L58            10 S L31 AND L32-L51
L59             9 S L57 AND L58
L60             9 S L59 AND PHOTODYN?
L61             1 S L58 NOT L60
L62            10 S L58 AND (PHOTODYNAM? OR PHOTOSENS?)
L63            10 S L58-L62
L64            25 S L57 NOT L63
                  SEL DN AN L64 25
L65             1 S L64 AND E1-E3
L66            11 S L56,L63,L65
L67            24 S L64 NOT L66
L68          6260 S L35-L37
L69          6372 S L29,L68
L70         10750 S L32-L34
L71         12254 S L38,L39
L72         24193 S L25,L70-L71
L73          5121 S L69 AND L72
L74          4165 S L73 AND (PHOTODYNAM? AND PHOTOSENS?)
L75           175 S L74 AND QUENCH?
L76            44 S L75 AND (ADV/RL OR ADVERSE EFFECT OR ?TOXIC?)
L77            43 S L76 AND RADIAT?/SC,SX
L78            19 S L77 AND ADV/RL
L79            24 S L77 NOT L78
```

```
                SEL DN AN 7
L80             1 S L79 AND E4-E6
L81            12 S L30,L63,L65,L80 AND L20-L80

     FILE 'REGISTRY' ENTERED AT 15:08:21 ON 19 OCT 2004

     FILE 'HCAPLUS' ENTERED AT 15:08:42 ON 19 OCT 2004

     FILE 'WPIX' ENTERED AT 15:08:56 ON 19 OCT 2004
L82             1 S L30
L83         24784 S A61P027/IPC OR (B14-N03 OR C14-N03 OR B12-L04 OR C12-L04)/MC
                E R07431+ALL/DCN
L84            86 S E1
L85           143 S L21/BIX OR L22/BIX OR L23/BIX OR L24/BIX
L86           161 S L84,L85
                E R17497+ALL/DCN
L87            40 S E1 OR (E2/BIX OR E3/BIX OR E4/BIX OR E5/BIX)
L88           177 S L86,L87
                E RA1QSX+ALL/DCN
L89            61 S E3-E11 OR L27/BIX OR L28/BIX
L90             4 S L88 AND L89
L91             3 S L83 AND L90
                SEL DN AN L90 1 3
L92             2 S L90 AND E1-E4
L93             2 S L82,L92 AND L83-L92
                E LAVIE G/AU
L94            16 S E3
                E LA VIE G/AU
L95            14 S L94 AND L83-L89
L96             6 S L94 AND M782/M0,M1,M2,M3,M4,M5,M6
L97             2 S L93 AND L82-L96

     FILE 'WPIX' ENTERED AT 15:17:52 ON 19 OCT 2004

     FILE 'DPCI' ENTERED AT 15:18:04 ON 19 OCT 2004
L98             1 S L82

     FILE 'HCAPLUS' ENTERED AT 15:18:31 ON 19 OCT 2004
L99             2 S US5047435/PN
L100            2 S L99 AND L20-L81

     FILE 'WPIX' ENTERED AT 15:19:20 ON 19 OCT 2004

     FILE 'DPCI' ENTERED AT 15:19:54 ON 19 OCT 2004

     FILE 'HCAPLUS' ENTERED AT 15:20:04 ON 19 OCT 2004

     FILE 'MEDLINE' ENTERED AT 15:20:44 ON 19 OCT 2004
L101          320 S L20
L102          456 S L21-L24
L103          456 S L101,L102
L104          322 S L26
L105          424 S L27,L28
L106          424 S L104,L105
L107            0 S L103 AND L106
                E PHOTODYNAM/CT
                E E5+ALL
                E E2+ALL
L108         8610 S E36+NT
L109         4447 S PHOTODYNAM?(L)?THERAP?
L110         9572 S L108,L109
                E PHOTOSEN/CT
                E E53+ALL
```

```
L111       66520 S E11+NT
L112        4744 S L110 AND L111
                E  PHOTOSENSITI/CT
L113         223 S E55
L114         210 S E73
L115         238 S L112 AND L113,L114
L116          39 S L115 AND L103,L106
L117         453 S L112 AND (EYE+NT OR EYE DISEASES+NT)/CT
L118          31 S L117 AND L116
                E PORPHYRINS/CT
L119          69 S E5
L120          91 S E29
L121          37 S L119,L120 AND L117
L122          38 S L119,L120 AND L116
L123          44 S L118,L121,L122
L124           1 S L118,L116 NOT L123
L125          19 S L123 AND PY<=2002
                E LAVIE G/AU
L126          44 S E3,E4
                E LA VIE G/AU
L127          15 S L126 AND L101-L125
L128           0 S L125 AND L127
L129           4 S L125 NOT AB/FA

     FILE 'MEDLINE' ENTERED AT 15:28:40 ON 19 OCT 2004
L130          25 S L123 NOT L125

     FILE 'BIOSIS' ENTERED AT 15:29:50 ON 19 OCT 2004
                E LAVIE G/AU
L131          68 S E3,E4
                E LA VIE G/AU
L132          28 S L131 AND L25,L29
L133          17 S L131 AND 00520/CC
L134          29 S L131 AND (CONFERENCE OR CONGRESS? OR SYMPOS? OR MEETING? OR F
L135          12 S L134 NOT L133
L136          17 S L133 AND L134
L137          10 S L132 AND L136
                SEL DN AN 1
L138           1 S L137 AND E1-E2
L139          18 S L132 NOT L137
                SEL DN AN 3 7 8 11 13 18
L140           6 S L139 AND E3-E15
L141           7 S L138,L140 AND L131-L140

     FILE 'BIOSIS' ENTERED AT 15:34:15 ON 19 OCT 2004

=>
```